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TYPHOID

Clinical Analysis of Three Hundred and Sixty Cases

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ALTHOUGH typhoid has received great attention throughout the medical literature of the past two centuries, we have been impressed by the scarcity of statistical reviews concerning this disease during the past several years and more particularly since the advent of sulfonamide therapy. It is therefore the purpose of this paper to review the cases of typhoid seen at Charity Hospital, New Orleans, during the six year period from Jan. 1, 1939 through Dec. 31, 1944, and to emphasize the clinical expressions of typhoid bacillus infections as seen during this period. Because of the magnitude of the task and the limitations of space, no exhaustive review of the literature will be attempted. Our series of 360 cases should, however, include examples of the difficulties most often encountered by physicians called on to diagnose typhoid and treat the patients.

CLINICAL FEATURES

During the six year period chosen for this study, 1939 through 1944, there were 360 cases of typhoid that we find acceptable for this series, according to the following criteria: (1) a positive blood culture; (2) a significant or rising agglutinin titer; (3) a urine or stool specimen containing typhoid bacilli; (4) a postmortem examination with findings considered pathognomonic of typhoid.

Incidence.—That the yearly incidence of typhoid in the United States is showing a downward trend is demonstrated in table 1. Five times as many cases were reported in 1930 as in 1944. It may also be seen that six Mississippi Valley states, Missouri, Kentucky, Tennessee, Arkansas, Mississippi and Louisiana, while showing a declining incidence, are still reporting far more than their expected number of cases as calculated from either the number of states or

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the percentage of the population represented. This may be due in part, however, to geographic and climatic factors. As may be seen from the last column, the downward trend of the number of cases of typhoid at Charity Hospital is in keeping with the trend for the nation and the Mississippi Valley area.

TABLE 1.—*Incidence of Cases of Typhoid and Paratyphoid in the United States as Compared with That of Cases in Certain Mississippi Valley States* During the Past Fifteen Years and That of Cases at Charity Hospital During the Past Six Years*

Year	Number of Cases in U. S. A.	Cases in Mississippi Valley		Number of Cases at Charity Hospital
		Number	Percentage of Total Number of Cases in U. S. A.	
1930	27,201	6,527	23.99	
1931	26,459	6,859	25.92	
1932	26,618	7,069	26.56	
1933	23,349	5,333	23.99	
1934	22,217	5,329	23.94	
1935	18,355	4,221	23.02	
1936	15,898	3,737	23.51	
1937	16,033	3,931	24.51	
1938	14,903	3,270	21.94	
1939	13,099	3,097	23.69	129
1940	9,809	2,370	24.17	76
1941	8,601	2,023	22.36	55
1942	6,678	1,555	23.29	43
1943	5,540	1,212	21.88	33
1944	5,388	1,058	19.27	24

* Included are Missouri, Kentucky, Tennessee, Arkansas, Mississippi and Louisiana.

The incidence of typhoid, in contradistinction to what one would expect, was well distributed throughout the four seasons (table 2), although it reached its peak during January and February. The only factor which we can suggest as explanatory of this seasonal distribution is the influence of climate.

TABLE 2.—*Seasonal Incidence of Three Hundred and Sixty Cases of Typhoid at Charity Hospital*

Month	Number of Cases	Percentage of Total Number of Cases	Month	Number of Cases	Percentage of Total Number of Cases
January	40	11.11	July	33	9.17
February	45	12.50	August	33	9.17
March	32	8.89	September	30	8.33
April	16	4.44	October	27	7.50
May	22	6.11	November	35	9.72
June	27	7.50	December	20	5.56

Racial Distribution.—Of the 360 patients, 221 were white and 139 were Negroes. Inasmuch as this is roughly proportional to the numbers of white and Negro patients admitted during the same period, no significant difference in racial susceptibility to the disease is indicated.

Sex.—There were 90 white females, 72 Negro females, 131 white males and 67 Negro males. These data reveal that 55 per cent of our patients were males. This is readily understandable, however, when one considers that males, because of occupational and other factors, usually have greater opportunity of taking the causative organism into their bodies.

Age.—The age factor is also related in a general way to the opportunities for contact of the patient group. The disease is considered to be relatively rare in the very young and in the aged. In our group 2 patients were less than 1 year of age; one was a white male infant of 8 months, while the other was a Negro female infant of the age of 9 months. Both these infants were said to have been breast fed, and there was no known occurrence of typhoid in either family. The oldest patient in this series was a white man of 71 years. The average age

TABLE 3.—*Age Incidence and Mortality Rate in Three Hundred and Sixty Cases of Typhoid in Five Year Periods*

Age	Number of Cases	Percentage of Total Number of Cases	Number of Deaths	Percentage of Mortality Rate
0 to 5	24	6.67	1	4.17
6 to 10	48	13.33	3	6.25
11 to 15	63	17.50	3	4.76
16 to 20	68	18.89	6	8.82
21 to 25	49	13.61	10	20.41
26 to 30	43	11.94	9	20.93
31 to 35	24	6.67	4	16.67
36 to 40	16	4.44	3	18.75
41 to 45	6	1.67	1	16.67
46 to 50	6	1.67	2	33.33
51 to 55	5	1.38	1	20.00
56 to 60	2	0.56	1	50.00
61 to 65	4	1.11	1	25.00
66 to 70	1	0.28	1	100.00
71 to 75	1	0.28	0	0.00

for our group of patients was 29.4 years. Table 3 shows the incidence of cases in five year periods.

Distribution in the Community.—Of the 360 patients, 84 (23.33 per cent) lived in New Orleans. Inadequate data failed to reveal how many of these patients had recently been in rural communities. One hundred and twenty-nine lived on farms, while 90 lived in rural communities and were engaged in farm work, fishing, hunting or trapping.

Occupational Factors.—Slightly more than a third of the entire group were children. Of the 360 patients, 219 lived on farms or in rural communities, and most of these were farmers, farmers' wives or children. Those whose occupations were associated with rivers, lakes or swamps included 18 fishermen, 5 trappers and 3 swamp loggers. Two oyster openers also contracted the disease. Three nurses, 2 hospital attendants and 1 undertaker were included in this series. Other occupational groups represented in this group varied greatly.

Vaccination.—Data concerning immunizations were incomplete. It was determined, however, that 41 patients living in areas where typhoid was endemic were said to have received three doses of vaccine within sixty days of the time that their illness began. Of these, 27 were exposed to typhoid in their own homes.

Sources of Infection.—About two thirds of this group of patients came from rural communities. Many had inadequate screening and toilet facilities, while about one fourth of these lived on the river or along the bayous. Many of these gave a history of drinking water of a well or a stream. Forty-nine of the group had been exposed to typhoid among members of their family, while 26 others knew of cases in their community. Of the 3 nurses in the group, 2 had nursed typhoid patients, while the 2 hospital attendants and 1 undertaker had also been in contact with human sources of infection. Over half the group previously mentioned as fishermen, trappers and swamp loggers had at one time or another drunk water that was potentially infected. About 20 per cent of the 360 patients, nearly all of these from New Orleans, said that they did not know of any possible sources of infection.

Period of Incubation.—Data obtained from this study do not permit an accurate determination of the period of incubation. Most of the patients giving a history of exposure had multiple opportunities to contract the disease. The period of incubation is said to range from three to twenty-one days, with the mean incidence between the eighth and fourteenth days.[1] The fewer the organisms that have entered the intestinal tract of the infected person the more prolonged is the period of incubation; the larger the number of organisms in the causal dose, the shorter is the period of incubation.

Onset.—Historical data obtained from the patients regarding the onset of their illness were in many instances none too reliable. Thirty-nine of the 360 patients (10.8 per cent) were said to have experienced a sudden onset of the disease, usually beginning as a transient chill. Of the remaining 321 patients, apparently adequate historical information was obtained from 296. As shown in table 4, malaise, headache and anorexia were the predominant prodromal symptoms. Respiratory symptoms occurred in nearly half the patients. Many patients also complained of one or more of the other symptoms in addition to the predominating triad of complaints. Of those patients who did not date the onset of their disease from a chill, the duration of prodromal symptoms before they were known to have fever or were confined to

1. Musser, J. H.: Typhoid Fever, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery and Specialties, Philadelphia, F. A. Davis Company, 1940, vol. 15, p. 501.

bed varied from two to eighteen days, with an average duration of about eight days for the group. Undoubtedly many of these patients had an elevation of temperature before they were aware of it.

Cutaneous Manifestations.—Although a few patients complained of severe sweats, the skin was usually dry. The two commonest conditions of the skin among our group of patients with typhoid were

TABLE 4.—*Incidence of Prodromal Symptoms in Two Hundred and Ninety-Six Cases of Typhoid*

Prodromal Symptom	Number of Cases	Percentage
Malaise	268	90.54
Headache	249	84.12
Anorexia	236	79.73
Cough	119	40.20
Sore throat	117	39.53
Thirst or dry mouth	110	37.16
Restlessness	83	28.04
Early abdominal pains	63	21.28
Early diarrhea	30	10.14
Epistaxis	13	4.39

rose spots and bedsores. Table 5 indicates the incidence of rose spots in the two racial groups. Nearly every Negro patient presenting these lesions had light-colored skin. The rose spots seen on the white patients usually consisted of slightly elevated, rounded, pale pink spots, from 2 to 4 mm. in diameter. These spots, which blanched on pressure, characteristically appeared on the ninth day of the disease but were first observed in some instances as early as the fourth or as late as

TABLE 5.—*Incidence of Rose Spots Among White and Negro Patients with Typhoid*

Race	Number with Rose Spots	Number with No Rose Spots	Percentage with Rose Spots
White	92	111	45.32
Negro	19	112	14.50
Total	111	223	33.23

the twenty-first day of illness. The abdomen, the chest, the back, the extremities and the face were involved in that order of frequency. The face, however, was involved but 6 times (5.4 per cent), while lesions of the palms, the soles and the scalp were not observed. About one third (36) of these 111 patients had two or more crops of rose spots, each crop varying from four or five to forty or more spots. Individual crops of rose spots, which did not itch, usually lasted from two to five days and disappeared without leaving any trace. No hemorrhagic manifestations were noted.

Bedsores, usually over the sacrum, were present in 46 patients (12.78 per cent) and were merely indications of pressure and uncleanliness rather than pathognomonic lesions of typhoid. Multiple furunculosis was seen in 8 patients. Typhoid bacilli were isolated from furuncles of 3 of these patients. Herpes labialis was observed but 7 times (1.94 per cent), pneumonia being a complicating factor in 3 of these instances, and was most conspicuous by its absence.

Temperature.—Thirty-nine of our patients suffered a transient chill at the onset, while 69 others experienced a chill within the first few days of illness. Of the 108 patients that experienced chills at some time during the course of their illness, 72 (66.7 per cent) suffered multiple transient chills, sometimes two or three within twenty-four hours. The average number of days during which chills occurred in this group was 3.2. After the actual onset, which was frequently difficult to determine, the temperature characteristically began to rise by successive steps, usually reaching its maximum by the tenth day. There were apparently, however, a few instances in which the temperature rose suddenly and reached its peak within forty-eight hours, while in a few others the temperature curve was without any tendency toward regular progressive elevation. The maximum temperature, according to recordings in our series, varied from 102 to 108.8 F. and averaged about 104.2 F.

After the temperature reached its maximum by the so-called step-ladder ascent, it was found to maintain its height for approximately eleven days. During the ascent the daily variations were usually not more than 1 or 1.5 F. After the maximum was reached, however, the daily fluctuations averaged 2.2 F. while ranging from 1 to 4 F. Some of the wide variations were probably due to vigorous use of temperature-reducing measures.

After the period of continued fever, the high temperature began to have more pronounced remissions, usually in the mornings. Once defervescence had begun, the temperature, which always fell by lysis, required from three to eighteen days to reach normal, and the average number of days required for lysis to occur was 7.8. Forty-five patients without true chills complained of chilly sensations, nearly all of these occurring during the period of defervescence, when the daily variations in temperature were greater than at any other time during the disease. Thus it was found that the average duration of fever for the entire series exclusive of the cases in which death occurred was 31.5 days. The duration of fever varied from seventeen days in a few cases to one hundred and nine days in another.

Relapses were observed in 45 cases. The average time required for fever to reappear was nine days, but it varied from three to thirty-eight days. The duration of these relapses, ranging from five to thirty-nine

days, was 15.6 days. Second relapses, which did not vary essentially from the initial ones, were observed five times.

Neuromuscular Manifestations.—Nervous manifestations were common in our patients. Table 6 shows the incidence of various neuromuscular manifestations that occurred at some time during the disease of the group. Headache, insomnia and dizziness were relatively early symptoms, while headache, apathy, delirium, stupor and, at times, coma were observed later in the disease, and their severity was usually dependent on the severity of the toxemia associated with the disease. Pain in the neck, nuchal rigidity or other neurologic manifestations caused lumbar punctures to be done on 46 of these patients (12.78 per cent). One patient, a Negro youth of 17, was found to have an elevated level of protein in the spinal fluid and over 900 cells per cubic millimeter; culture of the spinal fluid yielded Eberthella typhi. He

TABLE 6.—*Incidence of Neuromuscular Manifestations in Three Hundred and Sixty Cases of Typhoid*

Manifestations	Number of Cases	Percentage
Generalized muscular aches and pains	328	91.11
Headache	325	90.28
Weakness and apathy	312	86.67
Pain in back	273	75.83
Stupor	261	72.78
Delirium	150	41.67
Insomnia	93	25.83
Dizziness	90	25.00
Coma	55	15.28
Pain in neck	49	13.61
Stiff neck	35	9.72
Psychosis	7	1.94

eventually recovered. Delirium was usually manifested by a low muttering, but mania, sometimes accompanied with delusions and periods of melancholia, was also seen. Seven of the group exhibited psychosis after all other evidence of disease had disappeared—an incidence of psychosis of 1.94 per cent. With some of them it was a month or more before sufficient improvement had taken place to warrant discharge from the hospital.

Other outstanding symptoms noticed during the course of the disease included generalized muscular aches and pains, pain in the back which in a few instances led to an admission diagnosis of pyelonephritis, and weakness. Weakness, the last to disappear, usually became less evident as convalescence progressed. Flexion contracture of the right hip, which responded to traction and physical therapy, was seen as a sequel in 1 patient, while transient paralysis of the lower extremities requiring physical therapy was observed in another.

Special Senses.—Severe aching or soreness of the optic muscles was not a complaint of the patients. Photophobia was noticed in less

than 5 per cent of the 360 patients. Conjunctival injection, in contradistinction to observations among a large series of patients suffering with endemic typhus fever,[2] was observed in but 3, while purulent conjunctivitis occurred in 1 patient. Transient partial deafness was a complaint of 5 patients, while tinnitus was a complaint of 19 (5.28 per cent). Otitis media developed in 5 instances (1.39 per cent), while mastoiditis necessitating surgical intervention was observed in 2 of these.

Respiratory Manifestations.—Some evidences of involvement of the respiratory tract were present in most of the patients. Coryza, sore throat and manifestations of bronchitis were commonest (table 7). Cough, present in 310 patients, was usually nonproductive, but mucopurulent sputum was raised by several and blood-tinged sputum was produced a few times, usually in patients with clinical and roentgenologic evidences of bronchopneumonia. Nosebleed, at times rather severe,

TABLE 7.—*Incidence of Respiratory Manifestations in Three Hundred and Sixty Cases of Typhoid*

Manifestations	Number of Cases	Percentage
Coryza	315	87.50
Cough	310	86.11
Sore throat	304	84.44
Rales	231	64.17
Pain in chest	216	60.00
Cyanosis	129	35.83
Epistaxis	75	20.83
Pneumonia	41	11.39
Pleurisy	6	1.67
Pleural effusion	2	0.56

was present at some stage of the disease, usually early, in 75 patients. Pain in the chest, a complaint of 60 per cent of the group, was frequently nothing more than a soreness and possibly due to the cough associated with bronchitis. Rales, showing great variation in character and number, were heard in about 65 per cent of the patients. Although associated with pneumonitis in some instances, they were more commonly an indication of some degree of hypostatic pulmonary congestion and were heard oftenest during the more severe stages of the disease. Pneumonia, most often thought to be due to secondary bacterial invaders, was present forty-one times, an incidence of 11.39 per cent. Pneumococci were isolated from the sputums of 3 patients. One patient presenting clinical and roentgenologic evidences of pneumonia was found from cultures of the sputum to have typhoid bacilli in the sputum. There were no ulcers in this patient's pharynx or larynx that could be demonstrated. Respiratory rates were increased, the maximum respira-

2. Stuart, B. M., and Pullen, R. L.: Endemic (Murine) Typhus Fever: Clinical Observations of One Hundred and Eighty Cases, Ann. Int. Med. **23**:520, 1945.

tions recorded averaging about 32 per minute in uncomplicated cases, and steadily increased (to 50 or more in 18 patients) when bronchopneumonia or severe intestinal hemorrhage developed. The incidence of other manifestations of involvement of the respiratory tract is indicated in table 7.

The symptoms and signs of involvement of the respiratory tract were present in severe enough forms to cause 154 of the patients (42.78 per cent) to be subjected to roentgenologic examination of the chest, several having two or more such examinations. In 98 of these 154 patients the roentgenograms were considered to show an entirely normal respiratory tract; in 1 the roentgenogram showed evidences of pulmonary tuberculosis, thought to be inactive. In 37 of the remaining patients the roentgenograms revealed bronchopneumonia, while the roentgenograms of the other 18 were interpreted as showing signs of peribronchial thickening or hilar enlargement.

Cardiovascular Manifestations.—Symptoms referable to the cardiovascular system were varied. During the first week of disease, before the temperature had reached its maximum, the pulse was most often slow in relation to the height of the temperature. The average maximum pulse rate during this period was, however, for those patients entering the hospital during their first week of illness, 96 beats per minute. A dicrotic pulse was detected in 119 patients (an incidence of 33.06 per cent), and characteristically it appeared after the temperature had completed its ladder-like ascent and while the toxic manifestations of the disease were evident. Dicrotism was first detected on the average on the thirteenth or the fourteenth day of illness and usually disappeared whenever the heart action became rapid but was first observed as early as the seventh and as late as the twenty-third day. One patient, a white man of the age of 42, survived his initial bout of fever lasting twenty-seven days without evidence of a dicrotic pulse being detected. During a remission, however, which occurred after seven afebrile days, he had a dicrotic pulse on the eleventh day of the relapse, and he died on the twenty-ninth day of the relapse, with evidences of bronchopneumonia in addition to heart failure associated with hypertensive heart disease. During the second and third weeks of the disease, when toxemia was usually most evident, our patients with typhoid usually showed an increase of pulse rate which was in many instances proportional to the degree of fever present at the time. If we exclude all cases with complications considered capable of causing an increase of pulse rate, which includes all the cases in which death occurred, the maximum pulse rate recorded at some time during the disease averaged 122 per minute but varied from 100 to 144 per minute. The average maximum pulse rate for the 360 patients was 130 per minute.

Blood pressure readings recorded early in the disease were usually within normal limits. In those patients whose blood pressures were recorded regularly, however, there was a gradual and consistent fall during the febrile course. Drops as great as 40 mm. systolic and 30 mm. diastolic, without evidence of contributory complicating factors, were observed in a few instances; however, the usual change was only about one half as great. Severe drops in blood pressure were detected in several patients experiencing large intestinal hemorrhages. Transitory elevations in blood pressure, about 15 mm. of mercury in each instance, were observed in 2 patients in whom intestinal perforations were developing; the elevation was observed to persist for two hours in one instance, and was known to be present for five hours in the other.

The heart sounds and rhythm were usually normal at the onset of the disease in our series of patients with typhoid. During the more severe stages of the disease, however, a systolic murmur, usually soft and blowing in character, was heard in 112 patients (31.11 per cent). This murmur was heard oftenest in the mitral or the pulmonic area and was heard in both valvular areas in a few cases. Most of these patients had no evidence of heart murmurs when discharged from the hospital. In 32 patients (8.89 per cent) a rapid heart rate developed during the course of their illness, resulting in auscultatory findings which resembled embryocardia.

Clinical evidence of cardiac decompensation due to preexisting disease was seen in 10 patients. Five of these had hypertensive heart disease; 4 had evidences of arteriosclerotic heart disease, 1 with auricular fibrillation, and the remaining 1 was a Negro man of 29 who had syphilitic heart disease. Among the 6 of the 10 that died were 4 with hypertensive heart disease, 1 with arteriosclerotic heart disease and the Negro patient with syphilitic heart disease. Heart failure was apparently responsible for 3 of the deaths, while complications, such as intestinal hemorrhage or bronchopneumoia, were at least contributory causes of the other 3 fatalities.

Electrocardiographic studies were made on 16 patients, excluding those with preexisting heart disease, suspected to have myocarditis or some other cardiac complication. Of these 8 had only sinus tachycardia; 1 had slight right axis deviation; 1 had an abnormally long P-R interval (patient, 18 years of age, had a heart rate of 110 beats per minute when tracings were made); 1 had changes (slight elevation of S-T segments in leads I, II and III compatible with pericarditis), and 5 presented changes more consistent with toxic myocarditis. These changes included low T waves in all leads, inverted T_4 and notchings of R_2 at the base of the upstroke. Most of these patients had evidences of cardiac weakness during the more advanced stages of the disease, but all recovered. There was, however, 1 patient not subjected to electrocardiographic

studies, a white man of 28 years, whose postmortem examination revealed toxic myocarditis and pulmonic and hepatic congestion in addition to typhoid ulcerations of the ileum. There were therefore 6 patients with evident myocarditis, an incidence of 1.67 per cent, among this group.

One example of endocarditis was found at autopsy. A 67 year old white man had the onset of his illness twenty-five days before his admission to the hospital and had shown considerable improvement in his condition until three or four days before his admission. Recurrent fever and malaise were complaints on admission, and two blood cultures were positive for E. typhi before death occurred on the sixth day of hospitalization.

Venous thrombosis was recognized but three times (0.83 per cent) among our 360 patients with typhoid. This incidence is considerably less than that generally reported in the literature.[3] Evidences of venous thrombi, involving the left femoral vein in 2 instances and the right

TABLE 8.—*Incidence of Certain Gastrointestinal Manifestations Seen in Three Hundred and Sixty Cases of Typhoid*

Manifestations	Number of Cases	Percentage
Anorexia	327	90.83
Abdominal tenderness	303	84.17
Constipation	283	78.61
Abdominal distention	275	76.39
Foul breath and sordes	249	69.17
Nausea and vomiting	196	54.44
Diarrhea	156	43.33
Gross intestinal hemorrhage	76	21.11
Intestinal perforation	7	1.94
Herpes labialis	7	1.94
Parotitis	2	0.56
Ulceration of upper part of gastrointestinal tract	1	0.28

popliteal vein in the third, were noticed during the third week of the patient's disease in each instance. Each patient recovered without any indications of pulmonary embolism taking place. One patient with occlusion of the left femoral artery was observed, but eventual recovery without sequelae was seen to occur.

Gastrointestinal Manifestations.—Although typhoid is a disease which is essentially septicemic in nature, the outstanding gross pathologic changes are usually related to the small intestine. It is to be expected therefore that gastrointestinal manifestations of typhoid should be frequent and in many instances dangerous to life. The incidence of the gastrointestinal manifestations among our 360 patients with typhoid is shown in table 8.

3. Bercovitz, Z. T.: Typhoid Fever, in Bercovitz, Z. T.: Clinical Tropical Medicine, New York, Paul B. Hoeber, Inc., 1944, p. 548.

Anorexia, frequently a prodromal symptom (table 4), was present in over 90 per cent of the patients. Distaste for food, clinically significant from the standpoint of therapy, became more pronounced as the disease progressed, but it was usually replaced by an increasing desire for food as defervescence took place.

Diarrhea, a prodromal complaint of only about one tenth of the patients, was present at some time during the illness of 156 patients. The duration and the severity of the diarrhea, which most often had its onset by the eighth or the ninth day of illness, varied greatly. Diarrhea of a not inconsiderable severity, lasting but two or three up to fifteen days or more, was seen and in a few cases was thought to be an outstanding factor in the exhaustive state which preceded death. In some cases stools, frequently with a foul odor and characterized by a pea soup appearance, were passed twenty or more times a day. Severe, protracted diarrhea was, however observed in only 89 patients, an incidence of about 25 per cent. Several of the group passed stools two or three times a day, which were soft or semiformed in character, but these passages were not considered to be examples of true diarrhea.

Constipation, occurring either throughout the course or at some stage of the disease, was a complaint of 283 patients, an incidence of 78.61 per cent. Among those patients in whom diarrhea did not develop constipation was most troublesome during the second and third weeks but frequently persisted until convalescence was well established. About two thirds of the patients suffering from diarrhea, excluding the ones who died, experienced constipation after diarrhea had ceased. In general, it may be said that constipation, while twice as frequent as diarrhea, was of much less clinical significance from the standpoint of complications leading to death.

Abdominal tenderness was detected in 303 patients, but only 70 patients (19.44 per cent) complained of abdominal pain, which was usually not of a severe nature. Both tenderness and pain were usually observed after the first week of illness had passed; they were present in all abdominal quadrants but were most characteristically located in the right lower quadrant. The location of abdominal tenderness, in some instances associated with pain, in patients with typhoid, as determined from 303 patients of this series, is indicated in table 9.

Abdominal distention was present at some time during the period of illness in 275 patients (76.39 per cent) but was usually not severe unless associated with profound toxemia or diarrhea. Meteorism was, however, a potential danger because of the fact that intestinal hemorrhage or perforation occurred oftenest among the patients with gaseous distention. In 30 patients abdominal distention was so severe that Wangensteen's suction apparatus was utilized to supplement measures routinely employed to relieve this condition. Seventy-six patients, 21.11

per cent of the 360 in this series, had at least one intestinal hemorrhage of sufficient volume to be detected macroscopically. The average duration of disease before hemorrhage was first detected was 15.7 days, but initial episodes of intestinal bleeding ranged from the seventh to forty-first day. In some cases the volume of blood lost was only moderate and seemed to have little influence on the progress of the disease, but a few patients suffered hemorrhages either so massive or frequent that the prognosis was materially changed. Although intestinal bleeding was not the responsible factor in many instances, 26 of the 76 patients (an incidence of 34.21 per cent) who suffered the loss of grossly visible blood from bleeding typhoid ulcers of the intestine eventually died. Intestinal hemorrhage occurred in all but 1 patient with intestinal perforation and was first detected before the perforation took place in all but 1 instance. From the available data it is indeed doubtful that periodic blood cell counts, especially erythrocyte counts, are of much value as an evidence

TABLE 9.—*Location of Abdominal Tenderness Among Three Hundred and Three Cases of Typhoid*

Location	Number of Cases	Percentage
Right lower quadrant of abdomen	158	52.15
Diffuse, generalized	69	22.77
Epigastric	25	8.25
Umbilicus	20	6.60
Left upper quadrant of abdomen	12	3.96
Right upper quadrant of abdomen	11	3.63
Left lower quadrant of abdomen	8	2.64

of intestinal bleeding. Both the anemia, which may be moderately severe during the period when intestinal hemorrhage is most prevalent (fig. 6), and the concentration of blood which frequently follows an appreciable loss of its fluid content make it apparent that hemorrhages of sufficient quantity to be reflected in the peripheral blood picture will usually be self evident. Although a daily determination of the urea nitrogen concentration in the blood may serve as a fairly reliable warning that intestinal bleeding has occurred,[4] it is probable that regular examination of the feces of each patient to determine the presence of occult blood will oftener indicate the presence of small quantities of blood. Chemical evidence of blood was found in the stools, which were repeatedly examined, of 52 per cent of the patients in this series, excluding 76 patients in whom gross hemorrhage was apparent.

Of 11 patients presenting clinical evidence suggestive of intestinal perforation, 2 were not subjected to surgical abdominal exploration or to postmortem examination. Another patient who did not receive the benefit of a surgical abdominal exploration was found at autopsy to

4. Ingegno, A. P.: The Elevated Blood Urea of Acute Gastrointestinal Hemorrhage and Its Significance, Am. J. M. Sc. **190**:770, 1935.

have a perforation of the ileum. Eight abdominal exploratory operations were performed and revealed 4 examples of perforation situated in the lower part of the ileum, 2 instances of perforation of the appendix and 2 instances in which pathologic changes were not found. There were, therefore, 7 proved instances of perforation, 5 of the ileum and 2 of the appendix, 2 others with a clinical picture strongly suggesting that perforation had occurred, and 2 in which surgical abdominal exploration failed to reveal the presence of intestinal perforation. The average duration of disease in those patients known to have a perforation was nineteen days, but this complication was seen as early as the twelfth and as late as the twenty-seventh day. Of the 8 patients who underwent surgical abdominal exploration, only 3 survived—1 with a perforation of the ileum, 1 with a perforation of the appendix and 1 of those patients whose examination did not disclose the presence of any perforation. In the other patient whose abdominal exploratory operation failed to reveal any perforation there developed, in addition to intestinal hemorrhage, diarrhea and meteorism of such severity that evisceration occurred at the site of the surgical incision on the eleventh postoperative day. Death occurred a few hours later. In summarizing, it may be said that of 7 patients known to have intestinal perforation, 5 with perforations of the ileum and 2 of the appendix, 5 died (a mortality rate of 71.43 per cent) and that only 3 of 8 patients subjected to surgical abdominal exploration left the hospital alive, indicating that the mortality associated with this procedure was 62.5 per cent.

Ulceration located in the upper portion of the gastrointestinal tract, which is thought to be an infrequent manifestation of typhoid,[5] was observed in but 1 patient of this series. Ulcers thought to be examples of typhoid ulceration were observed, in addition to intestinal ulceration with generalized peritonitis due to perforation, to be present in both the esophagus and the stomach at the time of the postmortem examination, which was performed about two hours after death had taken place, on the twelfth day of the disease.

Of the other gastrointestinal manifestations listed in table 8, foul breath, sordes and nausea, generally accompanied with vomiting, require little comment. These conditions were usually most evident during the time when the disease was at the height of its severity. Herpes labialis was infrequently observed, and suppurative parotitis, in each instance requiring surgical incision and drainage, was observed but twice.

Liver and Gallbladder Manifestations.—Enlargement of the liver, sufficiently great to be clinically evident was present in 91 of these patients, an incidence of 25.28 per cent. Unquestionably an indication

5. Holmes, W. H.: Bacillary and Rickettsial Infections, New York, The Macmillan Company, 1940, p. 185.

of cardiac failure in a few patients, these examples of hepatomegaly were in most instances considered attributable to the typhoid infection. Enlargement of the liver was usually observed after the first week of illness and most often persisted throughout the period of a marked elevation of temperature, but it usually became less evident as defervescence progressed. Jaundice, confirmed by determinations of the icterus index, was clinically apparent in but 13 patients (3.61 per cent of the group) and was associated with involvement of the bile passages in only 6 cases in which subsequent surgical or postmortem examination was performed. In contradistinction, however, the cephalin flocculation test,[6] which in each instance showed a strong (4 plus or 3 plus) reaction, indicated the presence of severe hepatitis in 3 of these 13 patients. Later cephalin flocculation tests done for 2 of these 3 patients after convalescence was well established were interpreted as negative.

There were in this series of 360 patients with typhoid but 10 who apparently had cholecystitis (an incidence of 2.78 per cent). Of the 10 patients, 3 had suffered no symptoms referable to involvement of the gallbladder, and there were only 4 known instances of associated cholelithiasis. Three patients subjected to necropsy had evidences of acute cholecystitis. In 4 of the other 7, during the course of their disease, clinical conditions suggesting cholecystitis developed, whereas 2 patients had apparently mild infections which did not suggest the presence of complicating factors. The last of the 7 patients, employed by a large dairy, was discovered, during a public health survey, to be a carrier of typhoid bacilli.

Each of the 7 patients whose illness did not terminate in death was found to have stools that contained typhoid bacilli after the disease had run its course. Specimens of bile obtained from each of these patients were cultured and yielded E. typhi. Four of the 7 patients were subjected to cholecystectomy. Although there was no death due to operation on the gallbladder, only 2 of the patients no longer passed typhoid bacilli in their stools after that procedure had been carried out.

It is surprising that the number of patients with clinically apparent cholecystitis (2.78 per cent of this group) and of carriers of typhoid bacilli (1.67 per cent in our series) is not greater than usually found. It is, from the bacteremic nature of the disease, inevitable that the gallbladder become infected in typhoid. Moreover, the typhoid bacillus, unlike many bacteria, such as the streptococcus and the pneumococcus, grows readily in a medium containing bile. An experiment by Gay[7] has shown that typhoid bacilli injected into the vein of a rabbit can be

6. Gutman, A. B., and Hanger, F. M., Jr.: Differential Diagnosis of Jaundice, M. Clin. North America **25**:837, 1941.

7. Gay, F. P.: Typhoid Fever Considered as a Problem of Scientific Medicine, New York, The Macmillan Company, 1918.

recovered within half an hour from the gallbladder. Certainly it would appear that the hematic dissemination of the typhoid bacilli in patients with typhoid is probably due in part to the passing of bacilli from the intestinal lesions to the liver by the portal vein. Therefore, every patient should have cultures made of the stools in an effort to determine whether typhoid bacilli are present after the disease has run its course. Three negative cultures are required prior to the patient's discharge in most localities.

Splenomegaly.—Physical examination of the 360 patients revealed enlargement of the spleen in 229 (63.61 per cent). This enlargement, noticed by the end of the first week of the disease in a not inconsiderable number of patients, usually rapidly disappeared as clinical improvement became apparent.

Genitourinary Manifestations.—Abnormalities referable to the genitourinary tract were not prominent. Nevertheless, there were 7 patients (1.94 per cent) thought to have a complicating pyelonephritis, while in 9 patients there apparently developed cystitis, an incidence of 2.5 per cent. Retention of urine in the bladder was observed but once, and, likewise, only 1 instance of the urine being retained in the renal pelvis was detected. There were, however, 81 patients of our series (22.5 per cent) who had typhoid bacilluria at some time during the course of the disease. Although a few of the organisms persisted for a time after the disease had run its course, there were apparently no true examples in this group of persons becoming typhoid carriers because of bacilli in the urine.

Pregnancy and Typhoid.—Six women of this series were pregnant at the time of their admission to the hospital. Four of these pregnancies, ranging from two to six months in duration, resulted in abortions which ranged from sixteen to thirty-five days after the onset of the disease, while the average duration of disease before the uterus expelled its contents was twenty-four days. The other 2 women, who were pregnant at the time of admission, expected to deliver within the next three or four weeks. In both instances the disease apparently hastened the onset of labor, but both infants were born alive. One of the infants was kept in the hospital for several weeks after the mother's recovery. The apparent reason for this was that the child showed abdominal distention, diarrhea characterized by stools of a pea soup character and enlargement of the spleen. Unfortunately no diagnostic laborataory measures were utilized for this patient who was not included among our 360 patients, all of whom had significant laboratory data or postmortem examinations.

LABORATORY DATA

Although about two thirds of these patients entered the hospital with a presumptive diagnosis of typhoid, great variations in the severity

of symptoms referable to the various physiologic systems of the body were seen. Consequently, this group of patients was subjected to a large number of laboratory tests. Blood cultures, determinations of agglutinin titers and cultures of urine and stools all were obtained for nearly every patient and were for many patients repeated several times. Blood smears in a search for malaria were done thirty-nine times. For 58 patients one or more determinations of the blood urea concentration were made; for 21, determinations of the icterus index; for 39, determinations of the blood sugar, and determinations of serum protein, albumin-globulin ratio, carbon dioxide–combining power and blood chlo-

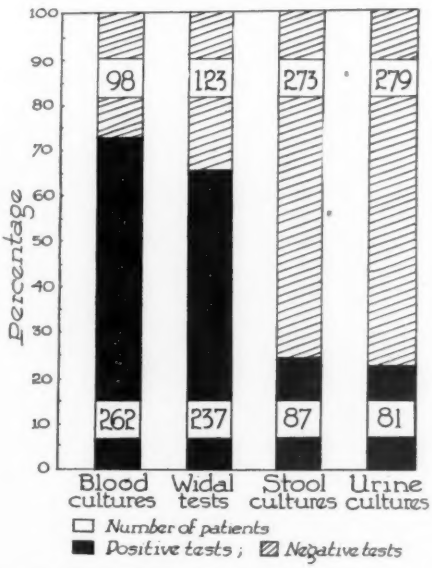

Chart 1.—The number and percentage of 360 patients with typhoid who had a positive blood culture, a positive Widal test, and stool and urine cultures showing the organism at some time during the disease.

ride and the cephalin flocculation test were each carried out in a few instances. The sputum of 28 patients was examined in a search for pneumococci, while 46 patients had surveys made of their spinal fluid. Other laboratory determinations, in addition to those discussed in the following paragraphs, were made infrequently.

Blood Culture.—A positive blood culture is the earliest and most conclusive laboratory evidence of typhoid that may be found. Of 360 patients, only 98 (fig. 1), most of those entering the hospital after the second week of illness, were not found to have typhoid bacteremia.

Blood culture should, however, not be delayed too long (fig. 2) because the incidence of positive blood cultures falls off rapidly as the disease progresses. The total number of blood specimens taken from our patients for culture was 832, and 336 of these (40.38 per cent) were positive (fig. 3).

Widal Agglutination Test.—Demonstrating the presence of agglutinins, so that when the serum from the blood of a patient with typhoid

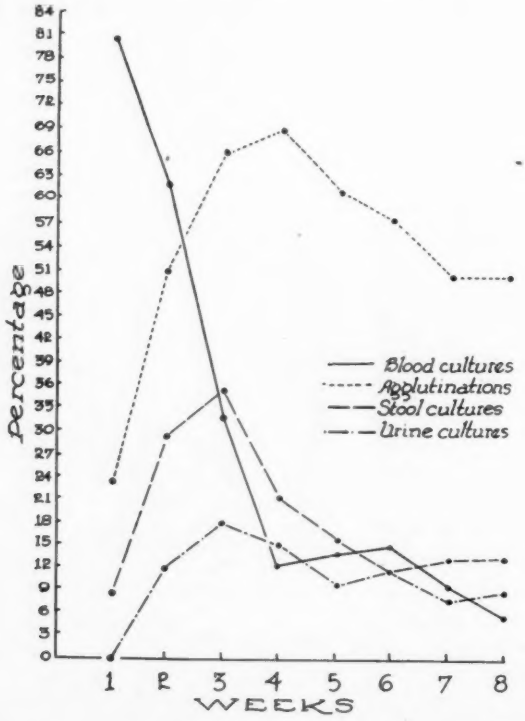

Chart 2.—A composite graph of the agglutinations and cultures for E. typhi of blood, stool and urine specimens from 360 patients taken at various intervals throughout a period of eight weeks.

is added to a culture of typhoid bacilli the agglutination test of Widal is obtained, is of great diagnostic value, but it has definite limitations. Thus it was found (fig. 1) that only 237 of our 360 patients (65.83 per cent) had agglutinins demonstrated in their blood serum at any time during the course of their disease. Whether or not this was due to the fact that the Widal reaction, frequently negative in the low titers usually employed to carry out the test, was not carried to a high titer

in these instances we were unable to determine. Figure 2 reveals the increasing incidence of positive Widal reactions as the disease progresses, but figure 3 shows that, of 933 Widal tests, only 546 (58.52 per cent) were positive in significant titers.

Cultures of Stools.—Only 87 of our patients had one or more positive cultures of stool (fig. 1), while only 318 of 1,442 cultures of stools (22.05 per cent) contained organisms (fig. 3). Typhoid bacilli were most often cultured from the stools of our patients during the third week of the disease (fig. 2).

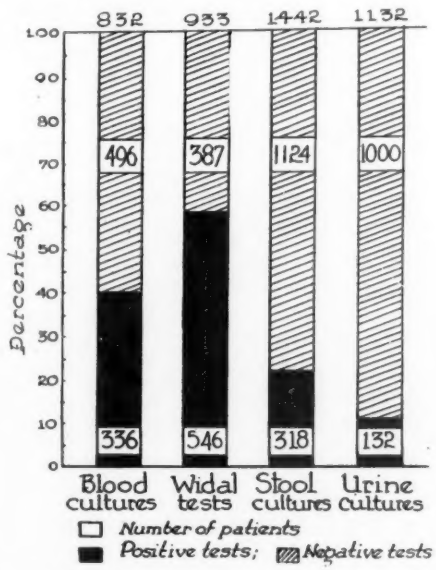

Chart 3.—The total number and the percentage of blood cultures, Widal tests and stool and urine cultures that were positive at some time throughout the illness of 360 patients.

Blood Picture.—While the cellular aspect of the blood is none too characteristic in many instances, it was found from an analysis of 721 white blood cell counts made for our patients (fig. 4) that there is usually a transient rise in the white blood cell count during the first ten days of the disease. Following this increase, a fairly rapid and progressive leukopenia, primarily due to a decrease in the number of polymorphonuclear cells, which results in a relative increase of the mononuclear cells of the peripheral blood (fig. 5), was found to reach its maximum severity at the end of the third week of the disease. Counts ranging from 1,200 to 20,000 cells were seen in apparently uncomplicated cases. Appreciable changes in the white cell count were usually lacking in

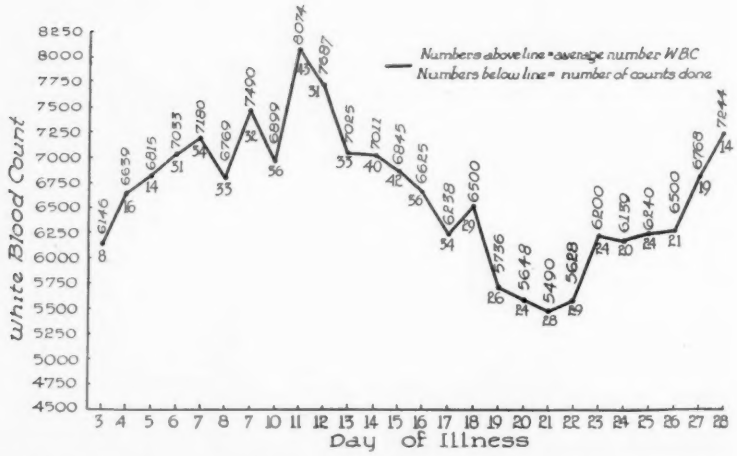

Chart 4.—Average white blood cell counts per day of illness of patients with uncomplicated typhoid, based on a total of 721 determinations.

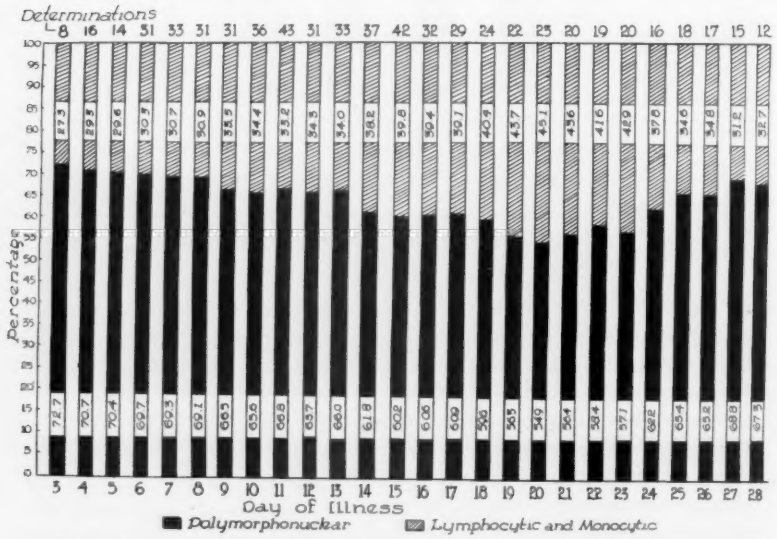

Chart 5.—Average ratio of polymorphonuclear to lymphocytic and monocytic cells per day of illness, based on 653 differential white cell studies. The total number of determinations is represented at the top of each column.

cases in which there was severe hemorrhage or intestinal perforation, complications which were most often seen during the period of relative leukopenia, which has been attributed to lesions of the red bone marrow.

Anemia was found to develop relatively rapidly among our 360 patients. Figure 6 shows the average red blood cell count per day, excluding those patients with gross evidences of intestinal hemorrhage. The maximum change in this count, too, was observed to occur at the end of three weeks and was followed by an increase in the erythrocyte count as convalescence was established.

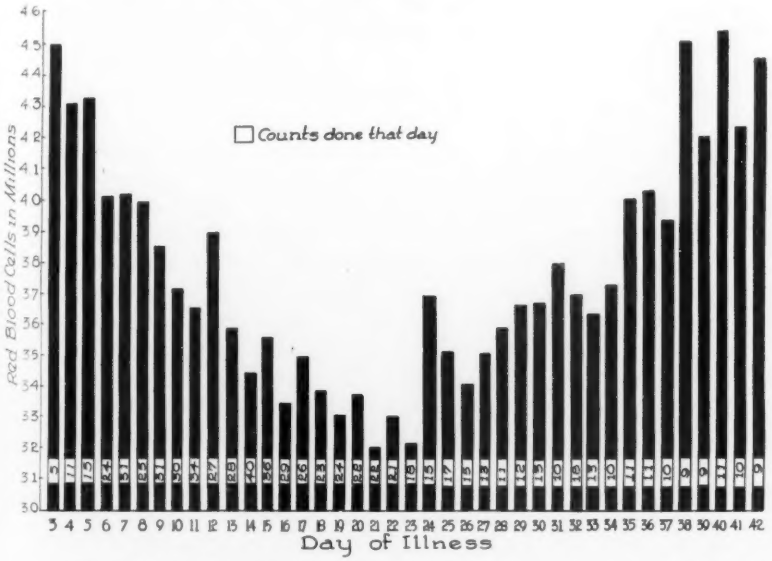

Chart 6.—Average red blood cell counts per day of illness of patients with uncomplicated typhoid, based on 749 determinations.

Urine.—Albuminuria was observed in 103 cases, an incidence of 28.61 per cent, in our series, and was usually transient in nature. Typically appearing late during the first week of illness, this transient albuminuria consistently cleared with convalescence. In a not inconsiderable number of these cases in which albuminuria occurred, casts, varying considerably in number and character, were also seen during the febrile course of the disease.

Serologic Examinations.—Serologic tests to determine the presence of syphilis were made routinely. In 11 cases the Kline and the Kolmer test were consistently positive, while in 3 instances (0.83 per cent) the serologic tests were positive during the febrile stage of the disease but became negative and remained so after defervescence occurred.

DIAGNOSIS

The diagnosis of typhoid depends on the demonstration of typhoid bacilli in the blood, the feces or the urine during some stage of the disease and on the development of a positive Widal reaction. When the disease is present in epidemic form, the clinical diagnosis may be strongly suggested by the symptoms presented, but even then it is necessary to have positive evidence of the nature of the disease in order to complete the diagnosis. It should be emphasized that a patient with typhoid, especially if seen after the fastigium is reached, is incapable of giving reliable historical data because of both the usually insidious onset and the increasing stupor, which makes it difficult to establish contact with the patient. Inadequate or unreliable historical information supplemented by a physical examination which fails to yield diagnostic information, then, is the problem which is too frequently encountered.

When one bears in mind certain characteristics of the disease, it is frequently possible to entertain a presumptive diagnosis of typhoid. Especially is this true during epidemics or in areas where cases of sporadic typhoid are known to occur. Typhoid is essentially an acute infectious disease, characterized usually by an insidious onset and a continued but gradual steplike rise in temperature, with a relatively slow pulse, which frequently becomes dicrotic unless a subsequent speeding-up of the pulse rate becomes manifest. Relatively severe headache, bronchitis, rose spots appearing in crops after the first week, splenic enlargement, leukopenia and anemia as the disease progresses and defervescence of the fever by lysis during the third or fourth week, when the various complications are oftenest seen, are also suggestive of typhoid.

Laboratory data derived from routine procedures other than the culture of blood, feces and urine and the utilization of the Widal reaction are not diagnostic of the disease. As previously shown (figs. 4, 5 and 6), leukopenia and anemia usually develop during the course of the disease. Albumin and casts are found in the urine of a not inconsiderable number of patients but are also evident among patients with other acute febrile diseases.

Of the specific laboratory procedures generally available, culture of the typhoid bacilli of the blood stream is by far the most conclusive proof of the nature of the disease. Especially is this true during the first week. In contradistinction, the Widal reaction, while of undisputed diagnostic aid, usually does not become positive until the second week of the disease, and sometimes even later, and in 34.17 per cent of our cases never reached a titer of significant diagnostic value (agglutination in a dilution of 1:160 or greater). Cultures of the feces and the urine, seldom revealing the presence of typhoid bacilli before the second or third week, may occasionally serve as conclusive proof of the

nature of the disease in question among cases in which the blood culture and the Widal reaction have failed, but they are certainly of more value in detecting those patients destined to become carriers of typhoid bacilli.

Infrequently the diagnosis of typhoid is established only by post-mortem examination. This was true in 1 of our cases, an instance in which repeated cultures of blood, feces and urine as well as the Widal reaction were consistently negative. Characteristic ulcers of the distal portion of the ileum and of the ascending colon were considered, together with swollen, soft, hemorrhagic lymph nodes of the mesentery and a considerably enlarged spleen, to be pathognomonic of typhoid. This impression was further confirmed by later histologic examination of tissues which had been removed for study.

Although 245 of our patients (table 10) were admitted to the contagious disease unit of Charity Hospital with a provisional diagnosis of typhoid, approximately 100 of them had been patients in other

TABLE 10.—*Admission Diagnoses in Three Hundred and Sixty Cases of Typhoid, as Divided into Various Groups*

Admission Diagnoses	Number of Cases	Percentage
Typhoid	245	68.06
Other acute infectious diseases	38	10.56
Diseases of respiratory tract	32	8.89
Diseases of genitourinary tract	18	5.00
Diseases of gastrointestinal tract	13	3.61
Diseases of central nervous system	7	1.94
Miscellaneous diseases	7	1.94

Louisiana state hospitals for one or more days before being sent to the New Orleans institution and had, when first seen at this hospital, conclusive laboratory evidence of the disease. If one considers this fact, it becomes evident that an initial impression of typhoid, established at the time of the patient's admission to the hospital without the benefit of diagnostic laboratory information, was recorded for only 40 per cent of our series of patients.

The admission diagnoses, divided into groups of diseases, such as the acute infectious diseases and diseases with symptoms referring predominantly to various functional systems of the body such as the respiratory system, which included sinusitis, tonsillitis, bronchitis, bronchopneumonia and lobar pneumonia, are recorded in table 10. The differential diagnosis of these conditions is beyond the scope of this discussion.

It should, perhaps, be mentioned as a warning that the occurrence of the anamnestic reaction, the reappearance of the agglutinins due to inoculation after many years under the nonspecific stimulation of some

nontyphoid disease, may lead to an erroneous diagnosis of typhoid in an occasional case. On the basis that the typhoid bacillus contains two antigens, termed respectively O and H, it has been found that the agglutinins which appear in a previously inoculated person as the result of a subsequent nontyphoid infection are of the H and not of the O type. In contradistinction, if the O type can be demonstrated in the blood, it is proof that the infection belongs to the typhoid group. Certain it is, therefore, that bacterial suspensions containing the O type of antigen are to be preferred in performing the Widal test.

COURSE

The average duration of typhoid among our patients before entering Charity Hospital was ten days, but the time of admission varied from the second day of the onset to the early stages of convalescence. If account is taken of the temporary hospitalization of some of these patients at other Louisiana state hospitals, however, the average duration of disease before the patients entered the hospital was only nine days. The average duration of hospitalization of the surviving group of patients was forty days, including a few who reentered the hospital because of a relapse; whereas an average of about fifty days elapsed between the onset at home and the day of discharge from the hospital. The different manifestations of the disease have been described in detail, while the various complications, many of which have already been described, usually became apparent as the disease reached its maximum degree of severity or else at about the time that defervescence had begun.

COMPLICATIONS AND SEQUELAE

Complications that occurred during the course of the disease among the 360 patients of this series or became apparent as convalescence developed are shown in table 11. These complications, a total of 308, which included 29 individual conditions, were observed among 193 of these patients, whereas in only 167 patients (46.39 per cent) did one or more complications of the disease fail to develop. Two or more complications, not infrequently resulting in death, were commonly observed; patients showing an undesirable response to therapeutic agents were also listed in the group of patients with two or more complications.

Most of the complications have been described in detail, yet only the incidence, the average time required for fever to appear and the average duration of the fever as determined among the 45 patients experiencing a relapse have been described thus far. A true relapse, presumably due to an overflow of typhoid bacilli from previously established foci in the bone marrow, is but a shortened repetition of the original disease. Typhoid bacteremia was demonstrated by culture methods in 40 of these 45 patients, yet rose spots were apparent in but 16 patients. Reduplica-

tion of most of the manifestations of typhoid as found to occur during the original episode, but usually of lessened severity, was observed. Intestinal hemorrhages, of no great prognostic significance, were grossly evident in 3 cases, while but one relapse terminated fatally.

ASSOCIATED NONTYPHOIDAL CONDITIONS

Diseases that either were present before the onset of typhoid or were not considered attributable to typhoid are listed in table 12. Of these, heart disease of hypertensive, arteriosclerotic or syphilitic origin, with apparent evidence of cardiac failure developing in 10 patients, was probably the most serious. Six of 11 patients that had clinically

TABLE 11.—*Incidence of Complications Occurring in Three Hundred and Sixty Cases of Typhoid*

Complication	Number of Cases	Percentage
Gross intestinal hemorrhage	76	21.11
Bedsores	46	12.78
Relapse	45	12.50
Pneumonia	41	11.39
Cholecystitis	10	2.79
Cystitis	9	2.50
Furunculosis	8	2.22
Intestinal or appendical perforation	7	1.94
Psychosis	7	1.94
Carrier state	7	1.94
Pyelonephritis	7	1.94
Premature delivery or abortion	6	3.70*
Toxic myocarditis	6	1.67
Otitis media	5	1.39
Transient deafness	5	1.39
Venous thrombosis	3	0.83
Reaction due to sulfonamide therapy	3	0.83
Mastoiditis	2	0.56
Serum sickness due to antityphoid serum	2	0.56
Purulent parotitis	2	0.56
Toxic hepatitis	2	0.56
Typhoid meningitis	1	0.28
Typhoid endocarditis	1	0.28
Arterial thrombosis	1	0.28
Evisceration of abdominal contents following surgical abdominal examination	1	0.28
Purulent conjunctivitis	1	0.28
Transient paralysis of lower extremities	1	0.28
Flexion contraction of right hip	1	0.28
Periostitis of rib	1	0.28

* This percentage is calculated from the total number of women (162) in this series.

detectable heart disease failed to survive. Diabetes mellitus, severe in nature, proved difficult to control and was contributory to the death of 1 patient. Pregnancy, as previously mentioned, resulted in either premature labor or spontaneous abortion in every instance. Of interest, but fortunately of no prognostic significance, were the apparent examples of diseases due to contacts occurring during hospitalization. These included measles (3 cases), scarlet fever (2 cases) and chickenpox (1 case). None of the other associated diseases exhibited any apparent influence on the typhoid infection, nor did the latter seem to affect them to any appreciable extent.

DEATHS

Forty-six of 360 patients died of typhoid, a mortality rate of 12.78 per cent. Twenty-two were Negroes, and 24 were white patients; 27 were males, and 19 were females. The mortality rate among the Negro patients was 15.83 per cent, compared with 10.86 per cent among the white patients; this may be of some importance with regard to prognosis in the two groups. An analysis of the deaths that occurred in the various age groups (table 3) reveals death rates roughly proportional to the different age periods: The mortality of patients under 21 years of age was 6.44 per cent; the death rate among patients from 21 to 40 years of age was 19.7 per cent, and 28 per cent of the patients over 40 years of age succumbed to the disease.

TABLE 12.—*Incidence of Nontyphoidal Conditions in Three Hundred and Sixty Cases of Typhoid*

Nontyphoidal Condition	Number of Cases
Ascariasis	12
Syphilis, all varieties	11
Heart disease	11
Pregnancy	6
Essential hypertension	4
Measles during convalescent period	3
Scarlet fever during convalescent period	2
Diabetes mellitus	2
Sickle cell anemia	2
Inguinal hernia	2
Pulmonary tuberculosis	1
Malaria	1
Chickenpox during convalescent period	1
Diphtheritic vaginitis	1
Gonococcal urethritis	1
Pelvic inflammatory disease	1
Benign nephrosclerosis	1
Gastric ulcer	1
Bilateral nephroptosis	1
Mental deficiency	1
Pernicious anemia with posterolateral sclerosis	1

The average duration of the disease before death took place was 25.8 days. However, 1 patient with typhoid of an unusually malignant nature died on the twelfth day as a result of generalized peritonitis which followed the perforation of an ulcer located in the terminal portion of the ileum. The longest period of time from the onset of the disease until death occurred was sixty-three days. The patient, the only one to die among those suffering relapses, succumbed on the twenty-ninth day of the second febrile period, which was separated from the initial twenty-seven days of fever by seven afebrile days.

Autopsies.—Of the 46 patients who died in this series, only 18 (39.13 per cent) were submitted to postmortem examination. Except in 1 case in which proof of the nature of the disease was lacking at the time of autopsy, the diagnosis of typhoid was established in these cases as follows: In 9 instances a diagnosis was made by

isolating typhoid bacilli from the blood stream by cultural methods—in 6 by positive blood cultures and positive Widal reactions, in 1 by a positive agglutination test alone, and in 1 by isolating typhoid bacilli from the blood, the feces and the urine on culture mediums. Among the patients who died but who were not subjected to postmortem examination the diagnosis of typhoid was established on the basis of the following laboratory data: positive blood cultures in 7 cases, positive Widal reaction in 1 case and cultures of the stool and the urine yielding typhoid bacilli in 1 instance, while in each of the remaining 18 cases in which postmortem examinations were not made typhoid was indicated by the results of two or more of the specific diagnostic laboratory measures available.

Apparent Causes of Death.—Typhoid is a bacteremic disease, yet the intensity of the general symptoms, such as fever, headache and malaise is an indication of septicemia, the toxemia being due to the liberation of endotoxin that occurs when the bacilli are destroyed in the circulating blood. Twelve different complications or associated diseases considered capable of materially affecting the prognosis of typhoid in our patients occurred a total of sixty-two times among the 46 patients who died of typhoid. In contradistinction, 7 patients died in whom none of these complicating factors were evident, as well as 4 additional patients, each of whom had several days before death an episode of intestinal bleeding which was so mild in nature that it could not be considered as of more than casual significance. The deaths of 11 patients, then, were apparently due to the severe septicemic nature of the disease. Although postmortem examinations, which failed to disclose more than intestinal ulceration, splenitis and swollen, soft, hemorrhagic lymph nodes of the mesentery, were done on but 4 of the 11 patients, we are attributing these deaths (23.9 per cent) to the overwhelming toxemia and exhaustion which were manifested in these patients. Intestinal perforation, despite surgical intervention in all but 1 patient, was followed by general peritonitis in each instance and was the probable cause of death in 5 (10.87 per cent). Grossly evident intestinal hemorrhage occurred in 26 of these 46 patients who died, an incidence of 56.52 per cent, but 7 patients suffered loss of blood in such quantity and with such rapidity that complete exsanguination, rapidly followed by death, resulted. Intestinal complications, therefore, consisting of perforation in 5 (10.87 per cent) and fatal hemorrhage in 7 (15.21 per cent) were responsible for death in 12 of the 46 patients (approximately 26 per cent). Six patients (13.43 per cent of those who died) had some variety of preexisting heart disease which was the basis for the subsequent myocardial failure that deprived them of their life. A reaction following the administration of sulfathiazole, which included a cutaneous eruption, hematuria and oliguria, was the apparent

lethal factor in 1 patient, while severe diabetes mellitus which resisted all measures directed toward its control led to the death of another patient. Myocarditis, a result of the action of endotoxins liberated from destroyed typhoid bacilli and circulatory insufficiency, severe pyelonephritis and typhoid endocarditis were each responsible for a death among our patients. Evisceration of the intestines through a surgical incision, present as a result of a fruitless surgical abdominal exploration carried out eleven days before, and complete exsanguination due to frequent hemorrhages were jointly responsible for the failure of another patient to survive. Pneumonia, present in 15 patients, was the sole complicating factor in but 2 of these patients and usually was thought to be a part of the terminal picture rather than its cause. As to the remaining 7 patients who died, intestinal hemorrhage, cholecystitis, pneumonia, pleural effusion, hepatitis and benign nephrosclerosis were the pathologic conditions that, as a result of two or more of these conditions exerting deleterious influences on a single patient, hastened death.

PROGNOSIS

The death rate determined by an analysis of the 360 cases of typhoid included in this study was 12.78 per cent. It should, however, be mentioned that this figure is perhaps too high, as these patients, many of whom applied for hospitalization because of the grave nature of their illness, probably do not represent a fair sampling of the population with typhoid which included patients that did not seek hospital care—the typhoid in many of these patients probably being of a mild nature that was not reported. The death rate among the Negroes of this series was about 16 per cent, compared with less than 11 per cent among white patients. The prognosis of typhoid in children not more than 5 years of age as determined from 24 patients in our series, which included 2 infants of less than 1 year, was better than that of typhoid in any other age group large enough to be of possible statistical significance. The prognosis of typhoid as determined from this survey is appreciably graver among Negroes, among patients beyond 40 years of age, among persons with some chronic illness, e. g., heart disease, and obviously for any patient in whom ominous factors, such as toxemia and exhaustion, perforation, hemorrhage, pneumonia and other serious complications, are prone to occur.

TREATMENT

Symptomatic and Supportive Therapy.—Although preventive measures have produced a progressive decline in the incidence of typhoid in the United States, little progress in regard to treatment, as shown by a 12.78 per cent death rate in this series, has been recorded in recent years. Considerable investigation has failed to provide a specific

therapeutic agent with which to combat typhoid, although Reimann and his associates [8] have recently discussed the administration of streptomycin to patients with typhoid and have reported favorable results in 3 of 5 patients treated with this agent. Treatment has, therefore, been directed toward providing general care, especially adequate nursing care and proper nutrition, yet a constant search for and prompt treatment of complications must be carried out. Prophylaxis, the prevention of the spread of infection to others, is also important and consists of such measures as prompt vaccination of all close associates of the patient, disposal of all excreta, care of linen and utensils and control of flies.

When typhoid is first suspected, the patient should be isolated and preventive measures should be utilized. The patient's room should be warm, well ventilated, quiet and screened. Rubber sheets, placed over a smooth mattress, and ordinary sheets, to be changed whenever soiled by the patient, aid in keeping the patient clean. Daily baths, supplemented by local cleansing after each bowel movement, are important, especially if followed by thorough drying and dusting with powders.

Bedsores, usually an evidence of pressure and uncleanliness, are largely preventable. Oral hygiene, including use of suitable mouth washes, cleansing of the teeth and the gums and application of cold cream to the lips, is important in avoiding such complications as stomatitis, parotitis and otitis media and should be carried out by the nurse whenever necessary. Constipation, a frequent complaint, is often avoided by daily administration of small enemas whereas cathartics, especially the more vigorous ones, should be employed with caution, since hemorrhage or perforation may follow. Measures to reduce high temperature and delirium are of extreme importance. Tepid or cool sponging should be given every three of four hours to patients with a temperature of more than 102 F., unless the presence of some serious complication is suspected. Cold water enemas may be helpful in an occasional case when the temperature is unusually high. An ice bag applied to the head may furnish relief from headache. Distention, at times avoided by the use of a proper diet, is sometimes relieved by eliminating carbohydrates from the diet for a day or so. The giving of enemas, the use of turpentine stupes, the insertion of a rectal tube and the passage of a stomach tube are all measures directed toward the relief of flatulence. Diarrhea, at times controlled by alteration of the diet, may necessitate the use of opium and a bismuth preparation in small doses.

Dietotherapy.—Adequate amounts of fluids are necessary; they were administered parenterally to patients in our series who were comatose.

8. Reimann, H. A.; Elias, W. F., and Price, A. H.: Streptomycin for Typhoid: A Pharmacologic Study, J. A. M. A. **128**:175 (May 19) 1945.

During the period of high temperature 5 or 6 liters of fluid a day, including nutrient liquids, are mandatory. A liquid diet of about 3,000 calories a day, served in small feedings at frequent intervals, usually every two hours, is used at Charity Hospital. This diet, intended to maintain the patient's normal weight, provides sufficient bulk in the form of carbohydrates, with proteins and fat in proportion, to reduce the incidence of constipation. The constituents of the diet most frequently used, in addition to strained fruit juices supplemented with 10 Gm. of lactose, include cereal gruel with cream and sugar, eggnog made with boiled milk, strained soups, malted milk made with boiled milk, jello with whipped cream, custard, chocolate milk made with boiled milk and occasionally weak tea or coffee with cream and sugar. The diet should, however, be altered to suit individual tastes, and after convalescence is established, a low residue diet high in protein and calories is used. Transfusions of citrated whole blood were given to about half of our patients and were thought to be indicated whenever medical or surgical shock, profound anemia, inadequacy of blood proteins or toxemia with exhaustion were imminent.

In order to correct possible deficiencies, the administration of supplementary vitamins is frequently indicated in the dietotherapy of the patient with typhoid and this for several reasons. Though typhoid is an essentially self-limited acute disease, the basal metabolic rate during the febrile stages is elevated to 30 or 40 per cent above the normal values for that patient. In addition, the dietary intake may be inadequate as a result of nausea and vomiting, anorexia or even mental disturbances, e. g., delirium and coma. Absorption, too, is impaired because of diarrhea. Some believe that oral or parenteral use of 30 to 100 mg. of ascorbic acid and 2 mg. menadione (synthetic vitamin K) daily will offset the tendency to bleeding. Therapeutic dosages of the vitamin B complex may be indicated.

Reimann [9] has outlined a satisfactory diet of 3,000 calories:

8 a.m.—Farina gruel: farina, ¾ cup; milk, ½ cup; cream, ¼ cup; salt
Toast, 1 slice
Butter, 1 tablespoon

10 a.m.—Cocoa, 1 cup

12 noon—Milk toast: milk, ½ cup; cream, ¼ cup; toast, 1 slice
Cream of pea soup, 1 cup
Egg, 1
Chocolate blanc-mange, ¾ cup
Butter, 2 tablespoons

2 p.m.—Malted milk, 1 cup

4 p.m.—Orangeade, 1 glass

9. Reimann, H. A.: Typhoid Fever, in Musser, J. H.: Internal Medicine, ed. 4, Philadelphia, Lea & Febiger, 1945, p. 28.

6 p.m.—Farina gruel, 1 cup
Milk, ½ cup
Toast, 1 slice
Butter, 1¼ tablespoons
Egg, 1
Cup custard, ⅓ cup
8 p.m.—Chocolate eggnog, 1 glass

Treatment of Intestinal Hemorrhage.—Absolute rest is necessary whenever intestinal hemorrhage is suspected or apparent. The stools should be examined closely for macroscopic or chemical evidences of blood, and determinations of blood pressure should be made at short intervals. Water may be given in small amounts, but food should be temporarily withheld. Opiates, which encourage flatulence, are best avoided, if possible, and should never be given until the question as to perforation has been answered. Morphine, in doses suitable to the individual patient, usually 0.015 Gm. (¼ grain) in adults, is the preferable drug. Stools should be passed with the least possible effort, usually on a large pad. Transfusions of whole blood are of value when bleeding has been severe enough to produce an appreciable degree of exsanguination. Coagulants, used extensively among 76 patients with intestinal hemorrhage in this series, were of no noticeable value. Feeding was in most cases gradually resumed when indications of bleeding were no longer present.

Treatment of Perforation, Peritonitis and Other Complications.—Perforation and peritonitis call for surgical intervention. Repair of the perforation, done as promptly as possible, represents the only chance of recovery. In this series 2 of 6 patients that had intestinal perforations repaired at the time of operation recovered, while the other 4 died of peritonitis and abscess formation. Cholecystitis subsides spontaneously in most instances. None of our patients were subjected to surgical drainage during an acute episode. However, cholecystectomy was later performed, in 4 because of the persistence of typhoid bacilli in the bile. Other complications, such as venous or arterial thrombosis, parotitis, otitis media, mastoiditis, furunculosis, failing circulation and pneumonia, were combated with the therapeutic measures usually employed when one is dealing with these conditions.

Chemotherapy.—Various chemotherapeutic and biologic agents were given to many of these patients, either in an attempt to find some agent with specific action against the typhoid bacillus or because pneumonia or some other condition that might benefit from sulfonamide therapy was present. Aminopyrine and quinine were used extensively, often together, in many of the earlier cases, yet they were of little value. Their most appreciable contribution was a bizarre temperature curve. Specific typhoid antiserum, used in 5 patients, failed to exert a favorable

TABLE 13.—*Comparison of One Hundred and Eleven Cases in Which Patients Were Given Sulfonamide Compounds with Two Hundred and Forty-Nine Cases in Which Patients Were Not Treated with Sulfonamide Compounds*

Drug	Number Cases in Which Sulfonamide Drug Was Used	Duration of Disease Before Admission, Days	Duration of Fever,* Days	Time from Onset Until Discharge,* Days	Duration of Treatment, Days	Relapses		Intestinal Hemorrhages		Pneumonia		Recoveries	Deaths	
						Number	Percentage	Number	Percentage	Number	Percentage		Number	Percentage
Sulfanilamide	9	10.44	26.25	43.90	6.50	0	0.00	2	22.22	1	11.11	8	1	11.11
Sulfapyridine	23	8.74	30.77	50.86	9.40	3	13.04	2	8.70	8	34.71	22	1	4.35
Sulfathiazole	35	9.48	33.03	51.47	11.59	7	20.00	7	20.00	4	11.43	33	2	5.71
Sulfamethylthiazole	6	9.80	27.20	41.00	12.50	0	0.00	1	16.67	0	0.00	6	0	0.00
Sulfadiazine	15	10.36	33.21	63.93	12.40	0	0.00	2	13.33	2	13.33	14	1	6.67
Absorbable group	88	9.56	31.38	52.69	10.69	10	11.36	14	15.91	15	17.05	83	5	5.68
Sulfaguanidine	8	6.50	60.25	82.25	10.00	4	50.00	0	0.00	0	0.00	8	0	0.00
Sulfasuxidine	8	9.25	37.00	67.50	11.50	0	0.00	3	37.50	0	0.00	8	0	0.00
Phthalylsulfathiazole	7	9.57	27.50	46.33	12.70	0	0.00	1	14.29	0	0.00	6	1	14.29
Nonabsorbable group	23	8.39	42.82	68.18	11.35	4	17.39	4	17.39	0	0.00	22	1	4.35
Treated group	111	9.31	33.75	55.89	10.83	14	12.61	18	16.22	15	13.51	105	6	5.41
Untreated group	249	10.44	29.17	47.28	0.00	31	12.45	58	23.29	26	10.44	209	40	16.06

* Cases in which death occurred are not included.

influence on the disease, while promin (sodium P, P′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) was administered without apparent benefit to 4 patients. Not one of the sulfonamide drugs was used frequently enough to yield information of statistical value, yet 111 of our 360 patients received one of the eight sulfonamide compounds (table 13) in therapeutically significant doses for a period of five days or more. Further analysis reveals that 88 of the 111 patients treated with sulfonamide compounds received a drug readily absorbed from the gastrointestinal tract, while the remaining 23 were given drugs that are poorly absorbed from the intestine. Serious complications, e. g., pneumonia, were, if anything, more prevalent among the "treated" patients. None of the 5 patients who died of intestinal perforation received sulfonamide compounds. By far the most significant information derived from table 13 is that from a comparison of the death rates of the two groups: 5.41 per cent for the group treated with sulfonamide compounds and 16.06 per cent for the other patients of the series. Removal of the 5 patients with perforation from the statistical groups, in an effort to evaluate the two groups better, reduced the mortality percentage of the control group only to 14.34. The sulfonamide compounds used among these patients had no apparent effect on the typhoid bacilli present in the feces. The longer duration of fever and hospitalization among the group of 111 patients was due to the fact that 2 patients became carriers of typhoid bacilli after recovering from clinically apparent attacks of cholecystitis. Pneumonia was more prevalent in the group treated with sulfonamide compounds because pneumonia was used as an indication for chemotherapy in several instances. There was no significant difference in the number of relapses in the two groups. Perhaps by chance the incidence of intestinal hemorrhage was smaller in the smaller group, and possibly it had some bearing on the comparative death rates of the two groups. A sulfonamide drug reaction, mild in 2 patients, was seen in 3 of the 111 patients and was probably responsible for 1 death. Interpretation of these data regarding sulfonamide therapy in typhoid indicates that while the sulfonamide compounds do not affect the severity or the duration of the disease they are indicated whenever secondary infections, e. g., bronchopneumonia, occur. In that connection, penicillin may also prove to be of limited usefulness in the therapy of typhoid.

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LATENT PHASE OF ASIATIC SCHISTOSOMIASIS

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THE PURPOSE of this report is to describe the findings in the "latent" phase of infection with Schistosoma japonicum and to evaluate the treatment. The study is based on observations of 300 patients admitted to Harmon General Hospital approximately six months after the onset of their acute illness overseas.

On Oct. 20, 1944, and for several weeks thereafter, American troops landed on the east coast of Leyte, one of the Philippine Islands. These troops were engaged in, or supported, active combat during the wet weather of the northeast monsoons. Conditions of combat during this period necessitated fighting, working, wading or bathing in polluted fresh water streams and rice paddies which harbored the snails serving as the intermediate host of S. japonicum. The schistosomiasis is transmitted to the mammalian host by the cercarias, which penetrate into the capillaries of the skin and enter the venous circulation. These larvae are then carried to the right side of the heart, the pulmonary capillaries and thence to the left side of the heart and the systemic circulation. Those cercarias which reach the portal circulation mature, migrate to the venules of the mesenteric vessels and mate. Within a few weeks thereafter the females are laying ova.

In from three to nine weeks after the cercarias enter the body the early symptoms of the disease appear. These consist of chills, evening fever (temperature, 99 to 105 F.), headache, lethargy, backache, nonproductive cough, abdominal discomfort and pronounced anorexia. In about one fourth of the patients in our series urticaria occurred at some time during the acute illness. Diarrhea developed in some and was neither bloody nor severe. Stupor, confusion, delirium and even paralysis, assumed to be due to the deposition of ova in the nervous system, developed early in a few patients. In rarer patients the constitutional symptoms were mild, and the diagnosis depended on the finding of ova in the stools. Enlargement and tenderness of the liver were common. The spleen was infrequently enlarged. Leukocytosis was usual, often

with an absolute eosinophil count as high as 20,000 per cubic millimeter of blood. The ova of S. japonicum were found first in the stools about seven and a half weeks after exposure.[1]

REPORT OF CASES

CASE 1.—The patient landed on Leyte on Nov. 15, 1944. There were repeated exposures in fresh water subsequently. In the middle of January 1945, loss of appetite, abdominal cramps, diarrhea, feverishness and a slight cough developed. When the patient was hospitalized on February 27, the leukocyte count was 12,300, with eosinophils 20 per cent. The stools contained the ova of S. japonicum. The patient was treated with fuadin, 45 cc., with partial relief of symptoms. In May 1945, because of the finding of ova in the stools again and because of continued occasional epigastric cramps, he was again treated with fuadin, 45 cc.

The patient was evacuated to the United States, and on July 29 he arrived at Harmon General Hospital, essentially asymptomatic. Physical examination revealed no abnormalities except for slight tenderness in the right upper quadrant of the abdomen. The leukocyte count on admission was 7,750 per cubic millimeter, with eosinophils 8 per cent. On August 10 the stool was found to contain the ova of S. japonicum. The patient was treated with 416 cc. of a 0.5 per cent solution of antimony and potassium tartrate. This therapy was completed on September 20. Subsequent examinations of the stool have revealed no ova and the patient has remained free of symptoms.

CASE 2.[2]—The patient landed on Leyte on Oct. 20, 1944 and was repeatedly exposed by bathing and wading in fresh water until December 1. On December 19 he had a temperature of 103 F., night sweats, headache, lethargy, stiff neck, backache and diarrhea. Later loss of appetite developed. On December 25 he noted weakness of his hands, so that he had difficulty in buttoning his clothes. On Jan. 6, 1945 cough began. Two days later the patient became so confused that he was unable to find his way over familiar routes near his tent. The next day he was hospitalized. It was stated that he was "mentally retarded and had flaccid paralysis of his arms. The results of physical examination were otherwise negative." By the next day urinary incontinence had developed. The spinal fluid was normal. Repeated examinations subsequently showed definite weakness and spasticity of all extremities but more marked in the arms. The reflexes were all hyperactive. Confusion and irritability persisted. Lesions developed on his extremities, suggestive of the presence of emboli. On January 17 the ova of S. japonicum were first found in the stool, and the leukocyte count was 28,300 per cubic millimeter of blood with eosinophils 61 per cent. Fuadin, 50 cc., was administered. His general condition improved rapidly. No further treatment was given overseas.

On April 27 the patient arrived at Harmon General Hospital much improved. He complained of weakness, particularly of his upper extremities, and loss of the finer movements of the fingers. Physical examination of the abdomen revealed no abnormality. Neurologic examination demonstrated muscular weakness of the upper extremities, particularly the left, and hyperactive tendon reflexes throughout.

1. Thomas, H. M., and Gage, P.: Symptomatology of Early Schistosomiasis Japonica, Bull. U. S. Army M. Dept. **4**:197-202 (Aug.) 1945.

2. The acute illness of this patient has been reported elsewhere (Johnson, A. S., Jr., and Berry, M. G.: Asiatic Schistosomiasis: Clinical Features, Sigmoidoscopic Picture and Treatment of Early Infection, War Med. **8**:156 [Sept.] 1945).

The leukocyte count on admission was 16,400 per cubic millimeter of blood, with eosinophils 9 per cent. The spinal fluid was normal.

On August 3 the stools were again found to contain the ova of S. japonicum, and the patient was treated with fuadin 105 cc., the course being completed on September 18. Since then repeated examinations of the stools have revealed no ova. By the time the patient was transfered from Harmon General Hospital on November 12 his neurologic abnormalities had noticeably improved, although he still experienced some difficulty in driving a car. The tendon reflexes were still hyperactive, particularly on the left side, and there was minimal weakness of the left hand.

CASE 3.—The patient landed on Leyte on Nov. 15, 1944 and bathed repeatedly in fresh water streams. During a survey of the unit, routine blood smears during February and March showed eosinophilia (percentage, 50). He was hospitalized

TABLE 1.—*Common Symptoms and Physical Findings During Acute Phase of Infection with Schistosoma Japonicum in 300 Patients*

Finding	Patients	
	Number	Per Cent
Fever	266	89
Chill	153	50
Sweating	163	54
Headache	208	67
Lethargy	183	61
Myalgia	194	65
Rotary stiff neck	150	50
Dry cough	196	65
Urticaria	82	27
Anorexia	273	91
Abdominal pain	274	91
Diarrhea	148	50
Palpable liver	133	44
Palpable spleen	41	14
Jaundice	29	10
Tenderness in upper part of abdomen	285	95
Loss of weight (average, 25 lb. [11 Kg.]—range, 5 to 55 lb. [2 to 25 Kg.])	300	100

on March 31, 1945, although he had no symptoms other than slight cough and slight loss of appetite. After repeated examinations, on April 6 his stools were found to contain the ova of S. japonicum and he was given a course of 50 cc. of fuadin. The maximal percentage of the eosinophils in the white cell count during this period was 42.

On admission to Harmon General Hospital June 7 he was asymptomatic except for mild loss of appetite and "nervousness." Physical examination showed no abnormality. The ninth examination of the stools, on July 25, revealed the ova of S. japonicum. At this time the leukocyte count was 11,400 per cubic millimeter, with eosinophils 16 per cent. The patient was treated with 320 cc. of antimony and potassium tartrate. Subsequent stools on repeated examinations have contained no ova. The patient continues to be asymptomatic.

An analysis of the symptoms and findings recorded in the early stages of the disease in the first 300 patients admitted to Harmon General Hospital is presented in table 1. This information was obtained from the patients and from the complete overseas records returned to the United States with many of the patients. Some of these case histories

have already served as the basis for excellent reports by overseas observers [3] and do not represent new data. They are presented in this paper largely for comparison with the findings on evaluation of the status of the patient's infection at the later phase of the disease when he came under our observation.

METHODS OF STUDY

On his admission to the hospital, each soldier gave a complete history and had a physical examination and certain laboratory tests. The hemoglobin content, the erythrocyte count, the erythrocyte sedimentation rate, the urinalysis and the nonprotein nitrogen level of the blood were recorded in all cases. Electrocardiograms were made. Studies of hepatic function including the excretion of sulfobromophthalein, a cephalin flocculation test, a quantitative van den Bergh test, a determination of the icterus index and plasma protein partition were carried out. Cutaneous tests with an antigen prepared from Schistosoma mansoni [4] were performed on most soldiers at different phases of the period of observation; the results will be reported separately.[5] Each patient was examined with the sigmoidoscope, and the first 50 patients admitted had roentgenologic studies of the colon. In addition a schedule of the examinations of the stool was planned to give each soldier the benefit of at least eighteen examinations at intervals over a ninety day period. During the first two weeks following admission six specimens were examined. If these contained no ova and there were no other contraindications, the soldier was given a thirty day furlough. At the end of this period he returned for another evaluation and again had six stool examinations over a two week period. If no ova were found, he was placed on furlough for an additional period of twenty days. On his return for final evaluation six specimens of stools were examined. If the stools again contained no ova, the soldier was returned to duty to be reevaluated after three months.

At the time of the writing of this report 111 patients have been discharged from the hospital with a known number of persistently negative stools. The average period of observation for these patients was four months (range two and a half to five); the average number of stools examined per patient was twenty-two (range fourteen to thirty-five).

The stools of all patients were examined by multiple direct smears, and those of some, by concentration methods, such as sedimentation, ether extraction and zinc flotation. A comparison of the results obtained by these methods will be presented in a separate report.[6] The direct smear technic detected six hundred sixty-three of six hundred and sixty-eight specimens of stool containing ova at the time of this analysis. A simple but time-consuming gravity sedimentation technic [7]

3. Billings, F. T.; Winkenwerder, W. L., and Hunninen: Studies on Schistosomiasis Japonica in the Philippine Islands, 1945, Bull. Johns Hopkins Hosp., to be published. Thomas and Gage.[1] Johnson and Berry.[2]

4. The S. mansoni antigen used was prepared by Mr. John Bozicevich and furnished through the courtesy of F. J. Brady, Surgeon, United States Public Health Service, the National Institute of Health.

5. Mitchell, L. P.: Skin Tests in Schistosomiasis Japonica, to be published.

6. Hesselbrock, W. B.; Lippincott, S. W.; Palmer, E. D.; Henderson, E. W., and Pauls, F. P.: Evaluation of a Serial Stool Examination Study in the Laboratory Diagnosis of Schistosomiasis Japonica, to be published.

7. United States War Department, Technical Bulletin (T B Med 167), Washington, D. C., Government Printing Office, June 1945.

used with one thousand and fifty-five specimens revealed only one third as large a percentage of the specimens containing ova as did the direct smear. In 2 of 42 patients the continued passage of eggs would, however, have been missed without the sedimentation technic. Although this is a laborious procedure, even a small increase in the specimens found to contain ova makes the procedure worth while, and adequate laboratory assistance should be available for its performance. In a small series of 29 cases in which a centrifugation-sedimentation technic [8] was available for comparison with the direct smear and gravity sedimentation technics, 4 patients were found to have eggs in the stools by a combination of the latter two methods and 3 more were added to the group by adding the new technic to the other two.

The need for multiple examinations of the stools is indicated by the fact that, of all the patients found with ova in the stools at the Harmon General Hospital, only 17 per cent had ova at the time of the first examination and 13 per cent still had no ova at the completion of the tenth examination. In at least 3 cases, more than twenty stool specimens were examined at the hospital before the ova of S. japonicum were found. Furthermore, the stools of approximately 10 per cent of the patients who had ova in their stools were not found to have them until the final period of observation. This fluctuation in extrusion of ova is well known and indicates the need for prolonged follow-up with multiple examinations of the stool by multiple methods.

If the patient's stools were found to contain ova, treatment was started immediately with trivalent antimony. The subsequent period of follow-up before discharge from the hospital was planned essentially as previously outlined. In 47 of the 57 cases in which a patient was discharged from the hospital as "cured" after treatment, the average number of specimens of stools containing no ova obtained prior to discharge was nineteen (range ten to thirty-four) over an average period of three and a half months (range two and a half to four and a half). Because of the facts previously discussed, all patients discharged from the hospital were arbitrarily advised to have reexaminations made every three months for one year. Only if further data on these patients are collected both in military and in civilian life will it be possible to say whether or not this period of follow-up was adequate. The maintenance in the Office of the Surgeon General of a complete list of the names of the infected soldiers evacuated to this country will supply a first step toward proper organization of this follow-up.

CLINICAL EVALUATION OF THE STATUS OF THE PATIENT'S INFECTION ON ADMISSION

On arrival at Harmon General Hospital the patients appeared to be in strikingly good physical condition. This was attributed to the good care obtained in overseas hospitals during the acute phase of the disease and to the recuperative power of the young American soldier who had had only a limited number of exposures to the parasite. None of the patients was acutely ill, although residual complaints of a relatively mild degree were present in 85 per cent and stools containing ova were obtained from 31 per cent on the initial evaluation (table 2).

8. Technique for Examining Stools for Schistosomiasis Japonicum Eggs: Method of Lt. Barody, Moore General Hospital, Swannanoa, N. C., 1945.

Ova occurred in 30 per cent of the stools from patients with complaints and in 38 per cent of the stools from patients without complaints. This seems to justify the use of the term "latent" for this phase of the disease. The general condition of all patients was such that in only 6 instances did furlough have to be delayed beyond the initial two week period of evaluation. In these there were neurologic complications.

The abdominal symptoms, present in 156 of the 300 soldiers, were limited to the upper part of the abdomen. They varied from an indefinite soreness to intermittent mild to moderately cramping pain in the region of either the liver or the epigastrium. The abdominal tenderness in the same region varied from mild to moderate. In some, the complaints simulated those of patients with low grade cholecystitis, peptic ulcer or hepatitis. In a few instances histories were sufficiently suggestive to

TABLE 2.—*Symptoms and Findings on Initial Evaluation of the Status of Infection in 300 Patients at Harmon General Hospital*

Symptoms and Findings	Number of Patients	Number with Ova in Stools
Abdominal discomfort	156	
Weakness	75	
	255	
Other symptoms (headaches, myalgia, nervousness)	186 (85%)	
No complaints	45 (15%)	17 (38%)
Palpable liver	32	
Palpable spleen	4	
Loss of weight	300 (100%)	93 (31%)
Total	300	93 (31%)

warrant roentgenologic studies of the gastrointestinal tract or the gallbladder. None of these studies revealed abnormalities. The liver was palpable in 32 patients. In most of them it was barely palpable or was felt only a centimeter below the costal margin; in 1 patient it was palpable 3 cm. below the costal margin.

HEMATOLOGIC STUDIES

The relationship of the total white blood cell count and the maximal percentage of eosinophils to the findings in the stool is presented in table 3. It is seen first that during the latent phase of the disease the maximal total white blood cell count and the maximal eosinophil percentage were much lower than in the acute phase. During the early period of illness only 22 per cent of the patients had had maximal white cell counts less than 10,000 per cubic millimeter of blood, and only 6 per cent had maximal eosinophil percentages less than 9. In contrast, during the latent phase 64 per cent of the patients had leukocyte counts below 10,000 per cubic millimeter, and 50 per cent had eosinophil percentages below 9. During the acute phase, there was no correlation between the

height of the leukocyte count or the eosinophil and the percentage of patients with stools containing ova, approximately 75 per cent in each group. During the latent phase no patient had pronounced leukocytosis, and the moderate rises of the leukocytes to levels between 10,000 and 20,000 per cubic millimeter of blood were not associated with increased incidence of stools containing ova. In other words, although moderate and marked leukocytosis was a common feature of the acute phase of the disease, in the latent phase stools with ova were no commoner in those patients with leukocytosis than in those patients with normal cell counts.

Striking eosinophilia was also more characteristic of the acute than of the latent phase. Although there seemed to be some correlation

TABLE 3.—*Relationship of Hematologic Findings to Results of Examinations of Stools in Acute Phase (Overseas) and Latent Phase (Harmon General Hospital) of Asiatic Schistosomiasis*

	Acute Phase (Overseas)			Latent Phase (Harlem General Hospital)		
	Cases		Per Cent with Ova in Stools	Cases		Per Cent with Ova in Stools
Maximal Total Leukocyte Count	Number	Per Cent		Number	Per Cent	
5 - 10,000	65	22	72	192	64	32
11 - 19,000	130	45	70	105	36	34
20 - 29,000	71	25	79			
30 - 50,000	21	8	81			
Total	287	100		297	100	
Average			75			31
Maximal Percentage of Eosinophils						
0 - 9	17	6	88	148	50	20
10 - 29	62	22	69	119	40	41
30 - 49	75	26	73	25	9	56
50 - 69	92	32	71			
70 - 99	41	14	80	3	1	0
Total	287	100		295	100	
Average			75			31

between the level of the eosinophilia and the likelihood of finding ova in the stool during that portion of the latent phase represented by our initial evaluation, the number of patients with marked eosinophilia who had no ova in their stools on the initial evaluation prevent the use of a high level of eosinophilia, e. g., 30 per cent eosinophils, as a direct measure of continuing activity of the disease.

At the time when ova were first found in specimens of stools at the hospital, the average percentage of eosinophils for 140 patients was 14, with a fourth of the patients having 20 per cent or more. Four to six weeks after apparently successful treatment, however, the average percentage of eosinophils for 45 patients was 6, with none having more than 20 per cent. Four to six weeks after unsuccessful treatment, in 32 patients the average percentage of eosinophils was 10, with 2 having more than 20 per cent.

It is apparent that there is some tendency for the percentage of eosinophils to stay elevated when treatment has failed to eradicate ova from the stool. However, in individual patients apparently treated successfully and followed for a longer period of time there may be occasional transient eosinophilia with percentages above 20. Because of this variation in patients treated with apparent success, an occasional increased eosinophil percentage is of no particular diagnostic value. In any given case, however, a persistently elevated percentage should suggest a more diligent than usual search for ova.

Studies of the erythrocyte sedimentation rate on admission of the patients showed an incidence of 33 per cent stools containing ova in 219 patients with sedimentation rates of less than 10 mm. in one hour and 53 per cent in patients with rates above 10 mm. There were, however, only 39 patients in the latter group. The hemoglobin values and erythrocyte counts of almost all patients were normal on admission. Anemia had occurred in only a small percentage of patients during the acute illness and had been corrected prior to arrival in the United States.

STUDIES OF THE LARGE INTESTINE

Proctoscopic examination was made of the entire group of 300 patients. In only 3 were intestinal abnormalities found. They occurred as single flat oval granulomas, 0.5 to 2 cm. in their longest diameter and moderately indurated. These were 7, 10 and 15 cm., respectively, from the anus. They were well demarcated, and the low grade inflammatory appearance did not extend to the surrounding normal mucosa. The surfaces of the lesions were grayish pink and appeared roughened. Passage of the proctoscope over the lesion produced minute areas of oozing hemorrhage; a sense of induration and roughness was imparted through the proctoscope to the examiner's sense of touch. Biopsy and histologic sections showed the characteristic ova in the submucosa surounded by chronic inflammatory tissue. In these 3 instances examination by direct fecal smear revealed ova; so the diagnosis of continued activity would have been made without proctoscopic examination. No elevated submucosal yellow nodules such as those described in the acute stage,[9] or papillomas such as those seen in late stages,[10] were observed in this group of patients in the early latent phase of the disease.

Roentgen examination after administration of a barium sulfate enema revealed no abnormalities of function or of structure of the colon in 50 patients who were thus examined.

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9. An Aid in the Recognition of Schistosomiasis Japonica, Bull. U. S. Army M. Dept. **4**:125 (Aug.) 1945.

10. Strong, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942, p. 1429.

FUNCTION OF THE LIVER

As a part of the initial examination, hepatic function was studied in approximately 250 of the patients. This seemed particularly indicated because of the symptoms in the right upper quadrant of the abdomen, the migration and final habitation of the parasite in the body, the occurrence of cirrhosis of the liver in repeatedly infected natives who were not treated, and the jaundice demonstrated or suspected in 10 per cent of the patients (table 1). It was also desired to use the results of the tests of hepatic function as a base line for studying the possible toxic effects of antimony on the liver. The following factors were measured: sulfabromophthalein retention, serum content of bilirubin, hippuric acid excretion, galactose tolerance and serum protein. In addition formaldehyde-gel tests were made. The detailed results will be submitted in a separate report; suffice it to say that on initial evaluation in this phase of the disease the percentage of patients with abnormal results was low. Of one hundred and forty-two initial determinations for 119 patients found to have stools containing ova at this hospital, 8 per cent showed sulfobromophthalein retention definitely increased (8 per cent or more). Of ninety-three determinations for 93 patients with stools containing no ova at this hospital, 13 per cent showed an increase of retention. Of the total of two hundred and thirty-five determinations, only 10 per cent showed 8 per cent or more retention. These abnormalities could not be correlated with the amount, the type or the date of previous treatment overseas.

Only 2 per cent of one hundred and thirty-two determinations of serum bilirubin in 129 patients with stools containing ova at this hospital showed 0.8 mg. per hundred cubic centimeters or more. Of one hundred and eighteen determinations for 118 patients with stools containing no ova at this hospital, 10 per cent showed an increase of bilirubin of this magnitude. These abnormalities could not be correlated with the amount, the type or the time of previous treatment overseas, but they did occur more frequently in those patients with abnormal retention of sulfobromophthalein than in those with normal excretion of this test substance. The other tests of hepatic function showed relatively few instances of definite abnormality and no correlation with the sulfobromophthalein or serum bilirubin tests. Evidence has been obtained, which will be presented separately,[11] that treatment with antimony and potassium tartrate may cause a transient disturbance of hepatic function.

Two patients in this series met accidental death while under observation. One had had repeated examinations of stools showing no ova over a period of five months prior to death. His liver was found sprinkled with miliary abscesses and fibrotic nodules surrounding schistosome ova. The total amount of liver tissue involved was small,

and the remainder of the organ was wholly unaffected.[11] The other, a patient who was under treatment with antimony and potassium tartrate because of ova in the stools, had had thorough studies of hepatic function with no evidence of impairment twenty-four days prior to death. His liver was similarly affected. How much damage of the liver will ultimately develop in this group of persons whose infection has been promptly diagnosed, who have been treated and removed from the endemic area, and who have been followed closely for failure of treatment and retreated if necessary is unknown. The natural course of the disease in untreated and frequently reinfected natives and the autopsy findings in the 2 cases reported make careful restudy of patients both in the army and in civilian life essential.

NEUROLOGIC STUDIES

The occurrence of neurologic complications during the acute phase of the disease has been previously reported.[3] In 8 of the 481 patients considered at this hospital to have schistosomiasis there was frank evidence of neurologic disorder.

According to the overseas histories of these patients, neurologic manifestations first appeared during the acute phase of the illness and were most severe at that time. There were headaches, nuchal rigidity and mild mental symptoms of lethargy and confusion. In 3 patients there was a sudden onset of the full-blown syndrome of disseminated encephalomyelitis. In 3 others stupor developed. Among the 8 patients, cranial nerve abnormalities were noted in 6. These included diplopia, pupillary abnormalities and facial weakness. In all 8 there was evidence of involvement of the motor tracts of the spinal cord, with weakness and spasticity affecting one or more limbs. Paresthesias and sensory disturbances were noted in 3 patients.

When the patients whose studies had been completed were discharged from the military service, they had received maximal benefit from hospitalization. They had all improved, but none was completely free of the symptoms or signs of his neurologic disorder.

In 5 additional patients with schistosomiasis there were lesions suggestive of peripheral neuritis. Whether the neuritis was coincidental or whether it was due to the deposition of ova in peripheral nerves or their nutrient vessels is unknown.

RESULTS OF TREATMENT

Overseas.—The relationship of the type and the amount of drugs received overseas to the presence of ova in the stool on initial evaluation

11. Lippincott, S. W.; Paddock, F. K.; Rhees, M. C.; Hesselbrock, W. B., and Ellerbrook, L. D.: Liver Function Tests in Schistosomiasis Japonica with Particular Reference to Antimony Treatment with Reports of Two Autopsies, to be published.

in Harmon General Hospital is presented in table 4. It is seen that 36 per cent of the patients given fuadin overseas had ova in their stools on reevaluation, compared with only 12 per cent of those given antimony and potassium tartrate. No apparent relationship was found to the amount of antimony given, although the criteria for choice of the varying amounts could not be determined from the records.

Treatment at Harmon General Hospital.—At the suggestion of the Chief of the Tropical Disease Treatment Branch of the Office of the Surgeon General, patients with ova in their stools were given, in rotation and without regard to previous treatment overseas, equivalent amounts of antimony (0.57 to 0.58 Gm.) in the form of either fuadin

TABLE 4.—*Relationship of Drug Used Overseas to Initial Findings in Stools at Harmon General Hospital*

Drug Used Overseas	Approximate Amount of Antimony, Gm.	Total Number of Patients	Number with Ova in Stools, Overseas	Number with Ova in Stools, H. G. H.	Per Cent with Ova in Stools, H. G. H.
Fuadin, Cc.					
10 - 29	0.17	18	17	2	11
30 - 49	0.35	127	88	49	39
50 - 69	0.52	31	24	12	39
70 - 89	0.70	30	21	8	27
90 -109	0.87	25	22	11	44
Total		231	172 (74%)	82	
Average					36
Antimony and Potassium Tartrate, Gm.					
0.5 - 1.0	0.27	6	3	1	17
1.1 - 1.4	0.45	3	3	0	0
1.5 - 1.9	0.61	25	21	3	12
Total		34	27 (8%)	4	
Average					12

or freshly prepared or commercially prepared antimony and potassium tartrate. Fuadin was given by injecting intramuscularly a 6.3 per cent solution on alternate days, beginning with doses of 1.5, 3.5 and 5.0 cc. and continuing with doses of 5.0 cc. until a total of 65 cc. had been given over a period of twenty-five days. Antimony and potassium tartrate, a 0.5 per cent solution, was given intravenously on alternate days, beginning with doses of 8, 12, 16 and 24 cc. and continuing with 24 cc. until a total of 320 cc. had been given in twenty-nine days. A complete record was kept of toxic symptoms by careful observation and daily questioning of patients. In addition, at a later date, 15 patients were treated with a course of 105 cc. of fuadin and 33 patients were given a course of 416 cc. of a 0.5 per cent solution of antimony and potassium tartrate.

The results of treatment are presented in table 5. The data indicate that antimony and potassium tartrate, either freshly or commercially

prepared, is far superior to fuadin in its immediate results, for 82 per cent of the patients treated with a single course of fuadin had ova in their stools again during the period of observation, compared with only 19 per cent of those given antimony and potassium tartrate.

Of those patients treated twice with fuadin, 69 per cent already have ova in their stools, although the follow-up period is not completed for any of them. Although no patients treated with the larger amounts of fuadin or of antimony and potassium tartrate have as yet again had ova in their stools, the follow-up period is too brief to justify conclusions. These patients are now being followed at another hospital.

The objection to the use of antimony and potassium tartrate in the past has been its reputedly greater toxicity as compared with fuadin. Over twenty-one hundred injections of a 0.5 per cent solution of antimony and potassium tartrate in a 5 per cent solution of dextrose

TABLE 5.—*Comparative Evaluation of Fuadin and Antimony and Potassium Tartrate in Patients Treated at Harmon General Hospital*

Drug	Amount of Antimony Given, Gm.	Number of Patients with Completed Evaluation Following Treatment	Number Whose Stools Contained No Ova During Follow-Up	Number Whose Stools Contained Ova During Follow-Up	Failures, per Cent
Fuadin (65 cc.), 1st course at H. G. H.	0.57	33	6	27‡	82
Antimony and potassium tartrate (320 cc.)	0.58	59	48*	11§	19
Fuadin (65 cc.), 2d course at H. G. H.	0.57	0	5†	11‖	69

* The treatment of 47 of these 48 patients was called a success, with an average of nineteen stools (range, ten to thirty-four) containing no ova over an average period of three and one-half months (range, two and one-half to four and one-half).

† The follow-up period has not yet been completed.

‡ The stools of 24 of the 27 patients again had ova when an average of seven stools (range, one to seventeen) had been examined over an average period of fifty-nine days (range, thirty-six to one hundred and eighteen days) after the completion of treatment.

§ The stools of 10 of these 11 patients again contained ova after an average of nine stools (range, eight to eleven) had been examined over an average period of seventy-eight days (range, forty-one to one hundred and four days) after completion of treatment.

‖ The stools of 10 of these 11 patients again contained ova after an average of four stools (range, one to ten) had been examined over an average period of forty-four days (range, thirty-four to sixty-one) after completion of treatment.

in isotonic solution of sodium chloride have been given to 102 patients without serious reactions. The precautions taken at the time of administration were (1) that the patient be recumbent during the injection, (2) that the drug be given slowly (not faster than 8 cc. per minute) and (3) that the patient remain in bed for one hour after its administration. Only minor toxic symptoms were encountered, and their incidence is presented in table 6. It is seen that cough, either occasional or frequent, nausea or vomiting and muscle and joint pains occurred more frequently in the patients given antimony and potassium tartrate

than in those given fuadin. It is further seen that there was no difference in regard to incidence of symptoms when freshly prepared antimony and potassium tartrate was compared with the commercially prepared drug. The administration of antimony and potassium tartrate and fuadin in longer courses reaching larger total amounts of antimony was associated with a higher incidence of frequent muscle and joint pains.

The cough which appeared after the administration of antimony and potassium tartrate occurred in almost all the patients and usually lasted for one to five minutes, beginning immediately after the administration of the maximal dose of 24 cc. Transient muscular stiffness, especially in the shoulders, and transient joint pains usually developed during the latter half of the course of treatment. The stiffness of

TABLE 6.—*Percentage Incidence of Minor Toxic Symptoms of Antimony and Potassium Tartrate and Fuadin*

	Antimony and Potassium Tartrate				Fuadin		
	Fresh, 320 Cc.	Commercial, 320 Cc.	Fresh, 416 Cc.	Commercial, 416 Cc.	1st, 65 Cc.	2d, 65 Cc.	3d, 106 Cc.
Number of patients	36	33	17	16	33	25	15
Cough	69	58	76	81	0	0	0
Frequent cough	33	30	24	19	0	0	0
Nausea	17	15	18	13	0	4	0
Vomiting	6	6	6	0	0	4	0
Joint and muscle pain							
Occasional	81	52	24	13	6	28	0
Frequent	0	3	65	81	3	28	100

muscles generally developed in from six to eight hours after administration of the drug and usually lasted for from ten to twelve hours. Occasionally it persisted during the following day. Movement of the upper extremities involving active motion of the deltoid muscles produced distress. There was no muscular spasm or tenderness.

Therapy had to be discontinued in 2 cases because of the severity of the symptoms. In a patient who had previously had two courses of fuadin nausea, vomiting and dizziness developed even with reduced doses of the drug. He was subsequently given antimony and potassium tartrate, but the course of injections could not be completed because of the development of considerable stiffness of muscles and, at the eleventh dose, weakness, pallor and bradycardia. A second patient who was receiving antimony and potassium tartrate had his medication discontinued because of immediate vomiting and weakness even with a reduced dose. He subsequently took fuadin without difficulty. In the treatment of a third patient the use of antimony and potassium tartrate was stopped after the fifth dose because of the development of jaundice,

although this was thought to be infectious hepatitis rather than a drug reaction. Patients in whom tests of hepatic function showed mild impairment were treated with both antimony and potassium tartrate and fuadin without any immediately recognizable serious results.

For 66 patients receiving antimony therapy in the form of fuadin and antimony and potassium tartrate, electrocardiograms were made before treatment and one hour after the second, tenth and fourteenth doses of fuadin and after the fifth, twelfth and fifteenth doses of antimony and potassium tartrate. The alterations in the electrocardiograms were limited entirely to changes in the T waves. No changes occurred in any of the other segments. No disturbances of rhythm were found. In several instances a slight slowing of the rate was noted, but no rate below 60 was recorded. The abnormality consisted of varying degrees of depression of the T wave. This occurred in one or more leads. Thirty-one per cent of the patients receiving antimony and potassium tartrate and 7 per cent of those receiving fuadin exhibited either isoelectric levels or sharply negative and even cove-planed T waves in three or more leads, with low voltage in the remaining lead. These alterations might easily have been interpreted as evidence of myocardial damage or even have suggested coronary occlusion. Gradual return to normal began several days after cessation of therapy and was complete on reexamination after thirty days in 90 per cent of the ptients.[12]

In view of the absence of evidence of serious cardiac or other significant toxicity, antimony and potassium tartrate in low concentration (0.5 per cent) appears to be the drug of choice as measured by the disappearance of ova from the stools. Since no differences were noted either in toxicity or in efficacy between freshly and commercially prepared antimony and potassium tartrate, the low cost of the former makes it preferable wherever the simple facilities necessary for accurate weighing and preparation of the solution are available.

CLINICAL STATUS ON COMPLETION OF PERIOD OF OBSERVATION

An analysis has been made of the records of 79 patients whose stools have remained free of ova of Schistosoma japonicum during three two week periods over an observation period of ninety days and of 15 patients whose stools similarly have contained no ova after completion of a single course of treatment at Harmon General Hospital. On completion of observation, approximately 90 per cent of the patients were free of symptoms, compared with only 15 per cent on admission (table 1). It is of interest that in a group of 71 patients whose stools were persistently free of ova at this hospital and whose records were available

12. Tarr, L.: The Effect of Antimony Compounds, Fuadin and Tartar Emetic, on the Human Electrocardiogram, Bull. U. S. Army M. Dept. 5:336 (March) 1946.

for analysis 42 per cent were symptom free at the end of their first furlough, approximately forty-five days after arrival here, compared with 15 per cent at the time of admission. However, the incidence of discomfort in the upper part of the abdomen which was 52 per cent at the time of the patients' admission was approximately the same at the time of their return from the first thirty day furlough. On completion of the observation period at the hospital, only 10 per cent of the patients had these complaints.

An analysis was made of the data on 92 patients who had completed a course of therapy and whose status had been reevaluated thirty days after completion of treatment. During treatment there was subsidence although not complete disappearance of symptoms. In many patients there was a gain of 3 to 4 pounds (1½ to 2 Kg.) in weight during treatment. During the thirty days of post-treatment furlough the patients began to experience the greatest relief of symptoms and to have a feeling of general well-being. Although the passage of time and the furlough itself contributed to this improvement, treatment was undoubtedly of importance. In general, the patients who received antimony and potassium tartrate were more commonly "symptom free," as a group, than those who had been given fuadin. It is difficult to say how much of this was conditioned by the rapidly spreading knowledge that a course of fuadin was less apt to free the stools of ova than a course of antimony and potassium tartrate.

COMMENT

Descriptions of Asiatic schistosomiasis [13] are derived, for the most part, from observations of patients who continue to live and to be reinfected in endemic areas where they receive no or inadequate treatment. The organization for the care of American soldiers has been such as to hold exposure to the minimum consistent with military exigencies, to treat the disease promptly and to prevent further infection. The system of continuing care through the period in which the patient is evacuated from forward areas to the zone of the interior has given an exceptional opportunity to record observations on the course of the disease in persons removed from the possibility of reinfection. In Army hospitals observations will continue to be made on patients whose disease has been proved to be active, until apparent cure is achieved. Observations on patients discharged from the army as "cured" should continue into civilian life. The data reported permit a description of the status of a group of patients observed for at least three months, approximately four to nine months after infection.

13. Faust, E. C., and Meleney, H. E.: Studies on Schistosomiasis Japonica, American Journal of Hygiene, Monographic Series no. 3, Baltimore, 1924.

At the beginning of the observation period at Harmon General Hospital, none of the patients were acutely ill, and their general appearance was such that it seemed that a hopeful prognosis for recovery could be offered. Approximately half of them still complained of abdominal discomfort and one quarter of some weakness. With continued observation for a three month period the frequency of these complaints decreased still further, so that only 10 per cent of the whole group of 300 had residual symptoms.

In spite of the strikingly good clinical appearance of the men on their admission to Harmon General Hospital approximately one third of them had the ova of S. japonicum in their stools. This high incidence of continuing activity may have been associated with the use of fuadin overeas, for analysis of the failure of treatment both overseas and in the hospital indicated that much better results followed the use of antimony and potassium tartrate. Although a final evaluation of these drugs requires a longer period of observation than is now available, antimony and potassium tartrate seems unquestionably the drug of choice. Its reputedly greater toxicity has not been observed since adoption of the procedure of injecting a 0.5 per cent solution slowly. In order to obtain a better evaluation of the final results, all soldiers discharged from this hospital with stools repeatedly containing no ova have been advised to have quarterly reevaluation for one year. The point at which one is justified in pronouncing them "cured" remains to be determined.

This need for caution in pronouncing these patients "cured" gains emphasis from the paradox that even though the chief criterion for the diagnosis of activity of the adult worms is the finding of ova in the stools the disease must be thought of as a generalized systemic one. The generalization of the acute phase, the occurrence of embolic neurologic complications and the habitation of the ova-positing worms in mesenteric venules whence eggs may be swept to the liver, all point to the necessity of continued careful observation of these patients. This should be done with the thought of disclosing evidence of activity and of hepatic dysfunction.

SUMMARY AND CONCLUSION

An analysis has been made of the clinical and laboratory findings in a group of 300 soldiers admitted to Harmon General Hospital four to nine months after the onset of illness due to infection with Schistosoma japonicum.

Although on admission to the hospital the majority of them had residual complaints, e. g., abdominal discomfort, weakness, headaches, myalgia and nervousness, their general physical condition was excellent.

In spite of previous treatment overseas, approximately one third of the patients had the ova of S. japonicum in their stools when the initial evaluation of their status was made at Harmon General Hospital.

Treatment with antimony and potassium tartrate (320 cc. of a 0.5 per cent solution) and fuadin (65 cc. of a 6.3 per cent solution), containing equivalent amounts of trivalent antimony (0.58 Gm.) resulted in the disappearance of ova from the stools in 81 and 18 per cent of the patients, respectively, during a period of follow-up averaging approximately three months. Since no major toxic effects were encountered with antimony and potassium tartrate in the concentration employed, it is clearly the drug of choice.

There is need for continuing a careful follow-up of these patients.

ADDENDUM

Since this paper was submitted for publication a continuing opportunity has been afforded to study the results of various treatment schedules. The evidence at present indicates that 444 cc. of a 0.5 per cent solution of antimony and potassium tartrate, U. S. P., is the most effective therapy. This is given intravenously on alternate days, beginning with 8 cc. and increasing the dose 4 cc. with each dose until a maximal dose of 28 cc. is given. The dose of 28 cc. is repeated every other day until 444 cc. (2.2 Gm.) of antimony and potassium tartrate has been received.[14]

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14. Most, H.: Personal communication to the authors.

CLINICAL NEPHROPATHIES IN EARLY SYPHILIS

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SYPHILITIC involvement of the kidneys, especially in early syphilis, has long been recognized. But the manifestations of a genuine syphilitic nephrosis or nephritis are so infrequent that even those who specialize in renal diseases may be confused by their occurrence. Because of this, it seems worth while to report our experience with syphilitic nephropathies at Bellevue Hospital. We have reviewed all of the cases of secondary syphilis treated in the wards of the hospital since January 1940. All of these patients were given some type of rapid treatment for syphilis. Twelve, or less than 0.3 per cent of those treated for secondary syphilis, showed markedly abnormal urinary findings which responded rapidly and dramatically to intensive, rapid treatment for syphilis. Ten of the 12 were girls or women. The cases are in accord with the description of early syphilitic nephropathies found in the literature. We have omitted from this report all instances of mild albuminuria prior to treatment.

One of the most comprehensive papers on clinical syphilitic nephropathies was written by Herrmann and Marr [1] in 1935. In 1934 Wosika and Thurmon [2] reported on syphilitic albuminuria. In later years reports have been made in this country by Baker,[3] Patton and Corlette,[4] and Klein and Porter.[5] Spanish and South American journals have

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1. Herrmann, G., and Marr, W.: Clinical Syphilitic Nephropathies, Am. J. Syph. & Neurol. **19**:1, 1935.

2. Wosika, P. H., and Thurmon, F. M.: Syphilitic Albuminuria, Am. J. Syph. & Neurol. **18**:2, 1934.

3. Baker, B. M., Jr.: The Relation of Syphilis to Nephritis, Bull. Johns Hopkins Hosp. **65**:196, 1939.

4. Patton, E. W., and Corlette, M. B.: Three Cases of Acute Syphilitic Nephrosis in Adults, Ann. Int. Med. **14**:1975, 1941.

5. Klein, A., and Porter, W. B.: Nephrosis Associated with Early Active Syphilis, South. M. J. **36**:694, 1943.

(Footnotes continued on next page)

published several articles on the same subject in recent years.[6] Both Stokes [7] and Moore [8] gave brief accounts of renal involvement in early syphilis and there can be no doubt that it occurs.

Herrmann and Marr [1] made an elaborate classification of early and late syphilitic nephropathies which is possibly more theoretic than real. But, if one chooses to label under separate headings every variety and degree of renal manifestation seen in early syphilis, an elaborate outline may be needed. With respect to the urine alone, early syphilitic nephropathies may simulate almost any known type of renal disease with the exception of pyogenic infections. When it comes to late syphilitic renal disease, we can say nothing because during the past ten years no patient has come to our attention for whom the diagnosis could be made. Such cases have been reported in the literature and, in view of the pathologic findings in kidneys of 19 patients with syphilis, described by Rich [19] in 1932, it is possible that late syphilitic nephropathies occur more frequently than we recognize them. We are at a loss, however, how to make the diagnosis unless manifestations of renal disease in late syphilis respond to antisyphilitic treatment. Such manifestations in our experience have been conspicuous by their absence.

CLINICAL MANIFESTATIONS OF EARLY SYPHILITIC NEPHROPATHIES

The urinary findings in early syphilitic nephropathies may vary from a mild albuminuria with few unusual elements in the sediment to a tremendous albuminuria associated with a few or a large number of casts. Red blood cells may be absent during the entire period of observation, or they may vary in numbers from an occasional cell to almost a gross hematuria. Because of this, early syphilitic nephropathies have usually been divided into syphilitic nephritis and syphilitic nephrosis. In our own experience the latter is commoner, but it is doubtful whether any distinct line can be drawn between the two in some cases.

NEPHROSIS IN SECONDARY SYPHILIS

The usual picture of early syphilitic nephrosis consists of a marked albuminuria, from 10 to 30 Gm. having been reported in twenty-four hour specimens. Some degree of oliguria is commonly associated

6. Luque, J. D.: Nefropatía sifilítica en el lactante, Rev. chilena de pediat. **14**:688, 1943. da Silva Mello, A.: Nefrites crônicas sifilíticas; um grupo autônomo de nefrites, Rev brasil. med. **1**:16, 1944. Jiménez Diaz, C.: La sifíles renal, Rev. clín. españ. **9**:145, 1943.

7. Stokes, J. H.; Beerman, H., and Ingraham, N.: Modern Clinical Syphilology, ed. 3, Philadelphia, W. B. Saunders Company, 1944, p. 603.

8. Moore, J. E.; Kemp, J. E., and others: Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941.

9. Rich, A. R.: Pathology of 19 cases of Nephritis Associated with Acquired Syphilis, Bull. Johns Hopkins Hosp. **50**:357, 1932.

with the albuminuria. The urine sediment contains casts but few or no red blood cells and the cylindruria is less noticeable as a rule than in cases of lipoid nephrosis due to other causes. Renal function is rarely impaired to any great extent. Mosenthal and Volhard tests usually show that the kidneys can concentrate and dilute the urine within normal limits, but elimination of the urine may be delayed. The nonprotein nitrogen content of the blood is not above normal. There may be some impairment of the urea clearance and the excretion of phenolsulfonphthalein. As a rule the patients complain of no subjective symptoms and, unless edema is present, the diagnosis is suspected only if routine urine examinations are made, and it is confirmed by the rapid disappearance of abnormal findings when antisyphilitic treatment is given.

Ten of the 12 cases reviewed by us were classified as belonging in the nephrosis group rather than that of nephritis. This decision may have been somewhat arbitrary. It was based on the predominating albuminuria with the presence of only a few or no red blood cells. In all but 3 patients, red blood cells ranging from an occasional cell to 7 or 8 in a high power field were reported at some time during the course of the involvement. Waxy casts were reported in 7 of the patients at the time of admission to the hospital. In no case was the blood pressure elevated. None had a secondary anemia and only 2 had any complaints referable to renal disease when admitted to the hospital. One complained of a dull headache associated with dizziness of two days' duration. The other stated that she had not voided in over twenty-four hours. When she was catheterized, 1,100 cc. of urine was obtained. The albumin formed a solid clot when the urine was boiled in a test tube, and numerous waxy casts were seen on microscopic examination.

In view of the presence of a few red blood cells in the urine of 7 of the patients in this group it is apparent that the glomeruli as well as the tubes are usually involved in the syphilitic process. As a matter of fact the urinary findings might suggest in some cases the nephrotic type of glomerulonephritis. Against this diagnosis is the relatively good renal function and the absence of much edema, although the latter has been reported in cases of secondary syphilitic nephrosis in the literature. All 10 of the patients observed by us were able to dilute and concentrate the urine within normal limits. None had more than 30 mg. of nonprotein nitrogen per hundred cubic centimeters. Urea clearance tests were done in 3 cases with only mild or no changes from normal findings. The plasma proteins were also within normal limits with normal albumin-globulin ratios. Excretion of phenolsulfonphthalein was only slightly diminished. The urinary findings became normal within four to eight days in every case. All 10 patients received rapid treatment for early syphilis. One received oxophenarsine hydrochloride alone. Six received daily injections of 0.06 Gm. of oxophenarsine and

fever was induced four times in ten days by the intravenous injection of typhoid vaccine. Three received penicillin, individual injections being given every three hours for sixty doses. One had a Herxheimer reaction with a temperature on the first day of treatment up to 104 F., but the urinary findings improved on the following day in spite of this. In no case was antisyphilitic treatment started with small doses of arsenical drugs or of penicillin because of the danger of a Herxheimer reaction. Therefore, from our experience, there is little to fear from Herxheimer reactions in secondary syphilitic nephrosis.

Because of the similarity of findings in these cases, there seems to be little reason to take the space or bore the reader with case histories of all 10. We have chosen 1 case for a detailed history, which follows:

REPORT OF A CASE

M. L., a 20 year old unmarried Negro woman, was admitted to Bellevue Hospital on Dec. 27, 1942. On admission her only complaints were a generalized rash associated with a sore throat of about two weeks' duration. Her past history included hay fever, which she reported having had in late July and August every summer since she was 9 years of age. In September 1940 she had a Bartholin cyst which was treated at Harlem Hospital. Her blood Wassermann reaction at that time was reported as negative. Her menstrual periods had been regular, the last regular period having ended about December 8. She stated that she noted vaginal bleeding again on December 25, but this stopped after one day.

On physical examination she did not appear acutely or chronically ill. She was well nourished. She had a generalized maculopapular rash on the face, trunk and extremities with numerous moist papules on the vulva. There were no mucous patches in the mouth or the throat, but the pharynx, pillars and tonsils were diffusely reddened. The eyes were normal except for a pigmented patch in the left fundus, due to an old traumatic chorioretinitis. Generalized adenopathy was present. The lungs were clear. The heart was normal in size and shape. The heart sounds were of good quality. No murmurs were present. The blood pressure on admission was 105 systolic and 70 diastolic, the highest reading throughout her stay in the hospital having been 124 systolic and 80 diastolic. The abdomen was not tender, and the liver and the spleen were not palpable. All deep reflexes were present. Vaginal examination showed some erosion of the cervix.

Laboratory Data on Admission.—Dark field examination of serum from the moist papules on the vulva showed many Treponema pallidum organisms. Smears for gonococci from the urethra and the cervix were negative. The blood Wassermann and Kahn reactions were strongly positive. The results of the urinalysis on December 28 were reported as follows: reaction, acid; specific gravity, 1.018; albumin (4 plus); sugar, none. Microscopic examination of the urine revealed many coarsely granular casts and numerous waxy casts, occasional white blood cells and 2 to 3 red blood cells per high power field. The blood cell count on the same day was: hemoglobin (Sahli), 80 per cent; red blood cell count, 4,180,000; white blood cell count, 13,600, with 63 per cent polymorphonuclear cells, 24 per cent lymphocytes and 1 large mononuclear cell. Results of an examination of the spinal fluid on December 30 were as follows: cells, 2 to 3 per cubic millimeter; amount of globulin, normal; total protein, 10 mg. per hundred cubic centimeters; Wassermann reaction negative, and gold curve, normal.

Course.—After the diagnosis of secondary syphilis, the patient was started on rapid antisyphilitic treatment with oxophenarsine hydrochloride. Our plan of therapy at that particular time called for two intravenous injections of 0.07 Gm. oxophenarsine hydrochloride each day for eight days. The patient was given two such injections on December 31. Then, as the urine report still showed a large amount of albumin and a few red blood cells per high power field, antisyphilitic treatment was stopped until a consultation could be obtained from the renal disease service of the medical department. It is unfortunate that the patient received some treatment prior to a thorough renal examination, because the latter was not obtained for several days after treatment was started and stopped. The abnormalities of the urine did not clear up rapidly after the two injections of oxophenarsine hydrochloride, but improvement was noted by the time the following laboratory data were obtained, three days after treatment was stopped.

Urea clearance was 95 per cent. The report on the urinalysis made on the same day was as follows: reaction, acid; specific gravity, 1.018; albumin (3 plus); sugar, none. Microscopic examination revealed numerous granular casts, numerous white blood cells and 1 to 2 red blood cells per high power field.

The nonprotein nitrogen of the blood was 20 mg. per hundred cubic centimeters. Results of the congo red test were negative. The plasma proteins were as follows: total protein, 6 Gm.; albumin, 3.2 Gm., and globulin, 2.8 Gm. per hundred cubic centimeters. Results of Mosenthal tests were within normal limits.

Antisyphilitic treatment with two injections of 0.07 Gm. oxophenarsine hydrochloride daily was resumed on January 7 and continued without interruption until the patient had received a total of sixteen injections. By the time that treatment was completed the urine was entirely free from albumin. The plasma proteins at the end of treatment showed a total protein of 6.6 Gm., the albumin being 4 Gm. per hundred cubic centimeters and the globulin 2.6 Gm. The nonprotein nitrogen of the blood was 17.2 Gm. per hundred cubic centimeters, and the urea clearance was 127 per cent when treatment ended.

On January 9 the patient was discharged for follow-up in the outpatient department, where subsequently the urine was found to be normal.

NEPHRITIS IN SECONDARY SYPHILIS

The chief distinction between early syphilitic nephritis and nephrosis is the relatively mild or moderate degree of albuminuria and the relatively pronounced hematuria in the former. We have classified 2 of our cases in the nephritis group. One of them simulated the focal type of glomerulonephritis rather than diffuse glomerulonephritis. The patient was a 19 year old Negro who had a fairly pronounced hematuria with innumerable red blood cells in every high power field on microscopic examination of the urine sediment. He had only a moderate albuminuria, the specimens examined before treatment being reported as giving a 2 plus reaction for albumin. Numerous granular casts were also reported. He had no hypertension or anemia and no subjective complaints. Renal function was not significantly disturbed. Antisyphilitic treatment with daily injections of 0.06 Gm. oxophenarsine hydrochloride and fever induced four times by typhoid vaccines, in a treatment period of ten days, reversed the urinary findings to normal.

The other patient was a young Negro girl who had what appeared to be a typical attack of diffuse glomerulonephritis which at first we believed was not due to syphilis. She had both hypertension and secondary anemia, together with moderate albuminuria and mild hematuria. Significant changes in the renal functions were also present.

The great improvement following penicillin therapy for secondary syphilis caused us to change our minds about the diagnosis. The case report follows:

REPORT OF A CASE

E. G., a 14 year old Negro girl, was admitted to Bellvue Hospital on Sept. 9,1944. The past history was negative for renal disease or any any other serious illnesses. About one month prior to admission she had been taken to Harlem Hospital because of pain in the lower part of the abdomen. From Harlem Hospital she was transferred to City Hospital, where diagnoses of gonorrhea and secondary syphilis were made. At City Hospital she received 20 Gm. of sulfadiazine for gonorrhea and three injections of oxophenarsine hydrochloride, 0.01 Gm., 0.02 Gm. and 0.04 Gm., respectively. She was then transferred to Bellevue Hospital for treatment with penicillin.

The physical examination, on admission to Bellevue Hospital, revealed a fading papular rash on the trunk and extremities with papules on the palms and soles. Generalized adenopathy was present. There was some tenderness in both lower quadrants of the abdomen. Otherwise the examination revealed no abnormalities except for a blood pressure of 180 systolic and 120 diastolic.

Laboratory Data.—The report on the urinalysis on the day following admission was: reaction, acid; specific gravity, 1.016; albumin (2 plus), and sugar, none. The microscopic examination revealed numerous granular casts and occasional hyaline casts; 50 to 70 white blood cells and 25 to 50 red blood cells per high power field. Similar findings were reported for the next seven days, during which time no antisyphilitic treatment was given and no sulfonamide drugs. Cultures for gonococci from the cervix and urethra were negative. The blood Wassermann and Kahn reactions were strongly positive. The nonprotein nitrogen of the blood on September 11 was 30 Gm. per hundred cubic centimeters. A blood count on the same day gave the following results: hemoglobin 9.3 Gm.; red blood cells, 2,970,000, and white blood cells, 9,600, with 68 per cent polymorphonuclear cells. The lowest specific gravity of the urine in Volhard tests was 1.004, and the highest 1.021. The rate of excretion was diminished (580 cc. in five hours after an intake of 1,500 cc. of water).

Course.—In view of the above observations, a diagnosis of diffuse glomerulonephritis was made. On September 15 treatment was started with penicillin; the patient received 20,000 Oxford units every three hours for sixty doses, over a period of seven and a half days. Daily determinations of blood pressure and urine-analyses were done throughout treatment, and Volhard tests were repeated during treatment and again on September 25. To our surprise definite improvement began to occur toward the end of treatment with penicillin. The blood pressure readings from the day preceding the onset of therapy to the time of discharge are as follows: September 14, 205 systolic and 140 diastolic; September 15, 170 systolic and 110 diastolic; September 16, 170 systolic and 120 diastolic; September 19, 185 systolic and 120 diastolic; September 20, 155 systolic and 100 diastolic; September 21, 160 systolic and 100 diastolic; September 22, 158 systolic and 100 diastolic; September 24, 145 systolic and 100 diastolic; September 26, 140 systolic and 90 diastolic;

September 27, 130 systolic and 82 diastolic; October 1, 115 systolic and 70 diastolic; October 2, 124 systolic and 70 diastolic; October 4, 120 systolic and 80 diastolic, and October 17, 120 systolic and 75 diastolic. Urinalysis showed similar improvement, both the albuminuria and sediment abnormalities clearing up, the hematuria having disappeared entirely by September 22, the last day of penicillin therapy. There was also improvement in the elimination and concentration tests.

The patient was discharged on October 18, at which time her blood pressure was normal and the urine showed only a trace of albumin with no casts. She was observed irregularly after her discharge, but on subsequent visits the blood pressure and urine were normal and the anemia improved. She was readmitted to the hospital on June 18, 1945, because of another attack of gonorrhea, for which she was treated with 150,000 units of penicillin. At that time her blood pressure was 125 systolic and 80 diastolic, and daily urine specimens examined from June 18 to June 27 were normal except for a faint trace of albumin.

DIFFERENTIAL DIAGNOSES

Obviously the diagnosis of a syphilitic glomerulonephritis was doubtful when the second patient whose case is reported was admitted to the hospital. It is still possible that syphilis may not have been the true cause of her nephritis. Nevertheless, in view of the course of the illness, we are unable to make any other diagnosis than that of glomerulonephritis due to secondary syphilis.

In contrast to this case, we have observed in 3 cases that glomerulonephritis was present at the time when the patients were given a diagnosis of secondary syphilis. None of these responded well to antisyphilitic therapy. One of them was treated with oxophenarsine hydrochloride and fever induced by typhoid vaccine without any appreciable exacerbation of the glomerulonephritis, but the patient continued to show the same manifestations during treatment and for some months thereafter, until he was lost from observation. He had a hypertension which persisted as did his mild albuminuria and hematuria. The other 2 were cleancut cases of diffuse glomerulonephritis. Both were treated with penicillin for secondary syphilis without any change in the renal function or urinary findings. In these cases secondary syphilis and nephritis were independent of each other.

Certainly, in the absence of hypertension and a history of previous renal disease, even a pronounced hematuria associated with secondary syphilis should be suspected as being due to the syphilis, but no certain diagnosis can be made prior to antisyphilitic treatment. The rare cases of secondary syphilitic nephritis were a real problem prior to the advent of penicillin. Today, however, such patients can be treated with relative safety by the use of penicillin. When a marked hemorrhagic nephritis is present, probably small doses of spirocheticidal drugs should be used initially to avoid a Herxheimer reaction. In the cases of milder disease, however, we have seen no cause for alarm in starting penicillin with doses of 20,000 to 40,000 Oxford units dissolved in water. Secondary

syphilis is almost never destructive and leaves no scar tissue as a rule. No sequelae have ever been reported for secondary syphilitic involvement of the kidneys, so far as we know.

The nephrotic type of involvement which has been observed by us is much more readily ascribed to secondary syphilis than the type simulating glomerulonephritis due to other causes. The noticeable albuminuria found in the former should in itself suggest the correct diagnosis. Prior to the advent of penicillin, when we treated large numbers of patients having early syphilis with arsenical drugs and fever induced by typhoid vaccine, albuminuria and sometimes hematuria occurred occasionally as reactions to the treatment. The urinary abnormalities were transitory and cleared up rapidly when treatment was stopped. The differential diagnoses between such reactions to treatment and urinary abnormalities due to syphilis is of course easy when the urine is reported normal prior to the onset of treatment.

In a previous publication [10] we reported several severe renal reactions which occurred following prolonged fever treatment produced by electropyrexia in combination with oxophenarsine hydrochloride. In these cases renal function was severely impaired, although fortunately all the patients recovered with no apparent sequelae.

SUMMARY

Early syphilis may involve the kidneys, simulating a nephrosis or glomerulonephritis. Of 12 cases of renal involvement in secondary syphilis reported, 10 were classified as syphilitic nephrosis and 2 as nephritis. In syphilitic nephrosis results of tests of renal function are not significantly abnormal as a rule, but pronounced albuminuria and cylindruria are present. In early syphilitic nephritis, there is less albuminuria than in nephrosis and more hematuria. In 1 case of diffuse glomerulonephritis apparently due to secondary syphilis, in which there was hypertension and secondary anemia, there was response to antisyphilitic treatment with penicillin. Early syphilitic nephropathies leave no demonstrable sequelae.

10. Thomas, E. W.; Wexler, G.; Schur, M., and Goldring, W.: Acute Nephrosis Complicating Two Day Arsenic and Fever Therapy for Early Syphilis, J. A. M. A. **122**:807 (July 17) 1943.

ASSOCIATION OF PNEUMONIA WITH ERYTHEMA MULTIFORME EXUDATIVUM

COMMISSION ON ACUTE RESPIRATORY DISEASES *
FORT BRAGG, N. C.

THE BENIGN form of erythema multiforme exudativum (Hebra) is a familar condition in medical practice.[1] Less common, but by no means rare, is the severe form of erythema multiforme exudativum with predominant involvement of the mucous membranes.[2] Case reports describing the latter condition have appeared with increasing frequency in recent years. The earlier impression was that patients showing predominant involvement of the mucous membranes were severely ill but rarely died. It is now apparent that such illnesses vary widely in severity, from mild to fatal. Whether or not the symptom complex to be described is merely a severe type of the benign afebrile form of erythema multiforme exudativum, which involves the skin primarily, is unknown.

The present report deals with a description of 6 cases of erythema multiforme exudativum with predominant involvement of the mucous membranes of the mouth, seen at the Regional Station Hospital at Fort Bragg, N. C., during a period of three years. In 3 of the 6 cases, clinical and roentgenographic evidence of pulmonary involvement was

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1. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939.

2. Keil, H.: Erythema Multiforme Exudativum: A Clinical Entity Associated with Systemic Features, Ann. Int. Med. **14**:449-494, 1940.

demonstrated. On the basis of the clinical and laboratory findings it was believed that the pulmonary lesions were due to nonbacterial pneumonia. The pneumonia appeared to be an integral feature of the disease and could not readily be considered a secondary complication. The chief purpose of this report is to emphasize the relationship of pneumonia to erythema multiforme exudativum, since it is a feature which has not been stressed sufficiently in previous descriptions of this condition. That such a relationship exists, however, is evident from a review of the literature, which reveals numerous examples of the occurrence of pneumonia in cases of erythema multiforme exudativum.[3]

Whether erythema multiforme exudativum is an etiologic entity is unknown. It has been regarded as a specific infectious disease, possibly of virus causation.[2] Apart from bacteriologic studies, however, little serious effort has been made to isolate an infectious agent by the inoculation of laboratory animals. Such an attempt was made with the present cases, and the results of these studies will be presented in this report.

HISTORICAL REVIEW

Several excellent reviews have pointed out the unity and relationship of the cases reported by many authors under a confusing variety of labels.[4] Unfortunately this knowledge is still not widely appreciated among internists, pediatricians, ophthalmologists, and dentists. All these specialists occasionally see cases in which there is predominant involvement of structures which bring the patient within the domain of their specialty. Accordingly a brief historical review is believed profitable.

In 1860 Hebra separated from the ill defined group of erythemas an entity which he called "erythema multiforme exudativum."[5] He did not describe lesions of the mucous membrane. Bazin enlarged the clinical picture by describing cases in which vesiculobullous stomatitis was present as well as cutaneous lesions.[6] He also noted the frequent

3. During the summer and fall of 1942, at the Boston City Hospital, Dr. Maxwell Finland studied several cases of erythema multiforme exudativum with pulmonary involvement. Some of us had the opportunity to see these cases. This experience stimulated our interest in the condition and aided in our subsequent recognition of similar cases at Fort Bragg.

4. (*a*) Keil.[2] (*b*) Klauder, J. V.: Ectodermosis Erosiva Pluriorificialis: Its Resemblance to the Human Form of Foot and Mouth Disease and Its Relation to Erythema Exsudativum Multiforme, Arch. Dermat. & Syph. **36**:1067-1077 (Nov.) 1937. (*c*) Lever, W. F.: Severe Erythema Multiforme: Report of Two Cases of the Type Ectodermosis Erosiva Pluriorificialis, with Development of Cicatricial Conjunctivitis and Keratitis in One Case, ibid. **49**:47-56 (Jan.) 1944.

5. Hebra, F.: Diseases of the Skin, translated and edited by C. H. Fagge, London, New Sydenham Society, 1866.

6. Bazin, E.: Leçons théoriques et cliniques sur les affections génériques de la peau, Paris, A. Delahaye, 1862; quoted by Keil.[2]

occurrence of fever and prodromal contitutional symptoms. In 1916 Rendu, and later others, described similar cases with fever, constitutional symptoms, and a vesiculobullous eruption involving lips, mouth, conjunctivas, glans penis and skin. They regarded this as a distinct entity, describing it as "erythema erosiva pluriorificialis."[7] In 1922, Stevens and Johnson reported 2 cases of this syndrome in a severe form and believed it to be a hitherto undescribed entity.[8] Subsequently the eponym "Stevens-Johnson" has been applied with increasing frequency in this country although it has no historical justification. Other descriptive labels used since then were "dermatostomatitis,"[9] "ulceromembranous stomatitis,"[10] and "mucocutaneous fever."[11]

CLINICAL PICTURE

An excellent summary of the clinical features of this disease is to be found in the review of Keil.[2] This author championed the point of view which emphasizes the unity of the benign and severe forms of erythema multiforme exudativum as varying manifestations of a single clinical entity. Erythema multiforme exudativum is a disease of short course, usually benign, characterized by a cutaneous eruption with a predilection for certain parts of the body, involvement of the mucous membrane, constitutional symptoms, seasonal occurrence, predominant incidence in young adults and recurrent attacks. There is no sex difference in the incidence of the disease.

The cutaneous lesions are of two types: erythematopapular and vesiculobullous. Lesions are most frequent on the dorsa of the hands and the feet, and they spread up the extensor surfaces of the arms to the sides of the neck and face and up the legs and thighs; they may be numerous or rather sparse. Not infrequently the scrotum is involved, but lesions occur on the trunk less commonly except in some of the cases of severer disease. Erythematopapular lesions are characterized by peripheral extension with recurrent efflorescence at the centers, giving rise to erythema iris lesions and their variants. Vesiculobullous lesions usually arise from the preceding erythematopapular type when

7. Rendu, R.: Sur un syndrome caracterisé par l'inflammation simultanée de toutes les muqueses externes (conjunctivale, nasale, linguale, bucco-pharyngée anale et balano-préputiale) coexistant avec une éruption varicelliforme puis purpurique des quatre membres, Rev. gén. de clin. et de thérap. **30**:351, 1916.

8. Stevens, A. M., and Johnson, F. C.: A New Eruptive Fever Associated with Stomatitis and Ophthalmia: Report of Two Cases in Children, Am. J. Dis. Child. **24**:526-533 (Dec.) 1922.

9. Baader, E.: Dermatostomatitis, Arch. f. Dermat. u. Syph. **149**:261-268, 1925.

10. Henry, T. C.: Ulcero-Membranous Stomatitis: Three Atypical Cases, Brit. M. J. **2**:273-276 (Sept. 5) 1942.

11. Haddad, N. N.: Muco-Cutaneous Fever, J. Canad. M. Serv. **2**:657-662, 1945.

the exudation of fluid is excessive. Both types of lesions are frequently present together. The bullous or vesicular lesion therefore is usually bordered by an erythematous halo. The vesiculobullous variety is more commonly associated with lesions of the mucous membrane and with fever and constitutional symptoms; hence it is more often seen by internists, pediatricians and ophthalmologists. Since the predominantly erythematopapular variety exhibits less, if any, fever or constitutional symptoms and less commonly involves the mucous membranes, it is more likely to be seen by the dermatologist or general practitioner.

Involvement of the mucous membrane is an integral feature of the disease. Its incidence has been estimated as approximately 25 per cent in all cases, and higher in the vesiculobullous variety.[2] In the latter cases, lesions of the mucous membrane may be the most prominent feature of the disease. Recurrent attacks in a single case may involve both skin and mucous membranes, skin only, or mucous membranes only.[12] As in the skin, lesions of the mouth begin with initial erythematous macules in which vesicles and bullae form. These quickly become eroded, leaving superficial ulcerations covered with white or grayish membranes bordered by zones of erythema. The lesions may be few and discrete, or confluent and involving the whole of the buccal, gingival and palatal mucosa and extending as well into the pharynx and below. Healing is eventually complete, without scarring, unless there is extensive secondary infection. This is likewise true in the skin.

Conjunctival involvement is common. Most often the inflammation is catarrhal and heals completely. In a number of cases it has been purulent or pseudomembranous, leading either to perforation of the cornea and panophthalmitis, necessitating enucleation, or to chronic infiltration of the conjunctivas and the cornea with scarring and adhesions.[13] Severe involvement of the eyes, usually associated with lesions of the mouth but occasionally with little or no involvement of the skin, has been reported.[14]

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12. (*a*) Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report of Two Cases in Children with Certain Observations on Histopathology and Animal Inoculation, J. Pediat. **121**:151-159, 1938. (*b*) Butler, J.: Erythema Multiforme Confined to the Mucous Membranes with Report of Case, Arch. Dermat. & Syph. **6**:1-5 (July) 1922.

13. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia: Atypical Erythema Exudativum Multiforme (Stevens-Johnson), Am. J. Dis. Child. **49**:1148-1160 (May) 1935.

14. (*a*) Koke, M. P.: Conjunctivitis in Erythema Exudativum Multiforme: Report of Three Cases, Arch. Ophth. **25**:78-88 (Jan.) 1941. (*b*) Bailey, J. H.: Lesions of the Cornea and Conjunctiva in Erythema Exudativum Multiforme (Hebra): Report of Three Cases with Grave Ocular Sequelae, ibid. **6**:362-379 (Sept.) 1931. (*c*) Kove, S.: Stevens-Johnson Syndrome (Eruptive Fever with Stomatitis and Conjunctivitis), Am. J. M. Sc. **210**:611-623, 1945.

Other mucous membranes and mucocutaneous borders involved include the nares and the nasal mucosa, the lips, the urethral meatus, the glans penis, the anus, the vulva and the vagina. Involvement of the larynx, the trachea, the bronchi and the bronchioles and the occurrence of pneumonia will be discussed presently.

Systemic manifestations are commonly absent in the erythematopapular variety confined chiefly to the skin, but may be rather severe in cases of vesiculobullous disease, especially those predominantly involving the mouth and other mucous membranes. Rather commonly prodromal symptoms suggestive of respiratory infection, such as sore throat, cough, coryza, headache, malaise and feverishness, precede by a number of days the development of the enanthems. This feature was prominent in some of the cases to be presented. Fever appears to follow no particular pattern; the temperature may be only slightly above normal or as high as 105 F., and the temperature may remain abnormally high for one or more weeks, usually returning to normal before the healing of the lesions is well advanced. In the cases of severer disease lesions of the mouth appear either initially or after several days of prodromal fever and symptoms. Conjunctival, nasal and penile lesions generally follow, and, in time of appearance, cutaneous lesions often are the latest active manifestations of the disease.

The course of the disease is variable. New cutaneous lesions may continue to form for periods of one to four weeks. Lesions of the mucous membrane, particularly those in the eyes, may persist for months, although this appears to be unusual. Apart from pulmonary involvement, visceral lesions do not appear to be prominent, if they occur at all. Periarticular swelling has been described but not true articular effusions. Febrile albuminuria is common, but obvious involvement of kidneys, heart, liver or other organs is not known to occur. Lymphadenopathy is not prominent. There seems to be no consistent or characteristic change in the formed elements of the blood. Both leukopenia [15] and leukocytosis [16] have been reported, the latter more frequently; most cases, however, exhibit normal total and differential leukocyte counts throughout the illness. Usually eosinophilia does not occur.[17] The few determinations of the chemical constituents of the blood that have been reported have yielded normal findings.[18]

15. (*a*) Stevens and Johnson.[8] (*b*) Fletcher, M. W. C., and Harris, R. C.: Erythema Exudativum Multiforme (Hebra)-Bullous Type: Cases Seen in a Contagious Disease Hospital, J. Pediat. **27**:465-479, 1945.

16. (*a*) Haddad.[11] (*b*) Fletcher and Harris.[15b] (*c*) Robertson, H. F., and Donovan, T. J.: Erythema Multiforme Exudativum or Bullosum, Mil. Surgeon **96**:259-262, 1945. (*d*) Rosenberg, L., and Rosenberg, J.: Erythema Exsudativum Multiforme (Hebra) with Conjunctivitis and Stomatitis, Arch. Dermat. & Syph. **41**:1066-1072 (June) 1940.

(Footnotes continued on next page)

PATHOLOGY

There is a paucity of information regarding the pathology of erythema multiforme exudativum due to infrequent opportunity for histopathologic examination. In the vesiculobullous variety, the skin on microscopic section contained bullous lesions, some of them desquamated, leaving superficial ulcers limited sharply to the epidermis and the upper corium.[19] Hanke [20] described intracytoplasmic inclusions in the conjunctiva; this observation awaits confirmation. The pathologic findings in the tracheobronchial tree and the lungs will be discussed subsequently. Other organs have shown only acute passive congestion.[21]

DIFFERENTIAL DIAGNOSIS

A number of diseases, at certain stages of their course, may exhibit pleomorphic erythematous eruptions, i. e. rheumatic fever, erythema nodosum, disseminated lupus erythematosus and bacteremia due to meningococcus and gonococcus organisms. Relatively few conditions, however, simulate the form of erythema multiforme exudativum characterized by vesiculobullous lesions of the skin and the mucous membranes. Among such diseases it is of importance to differentiate pemphigus. The distinction may be difficult, at times, but the age distribution of pemphigus, the development of bullae on apparently normal skin, positive Nikolsky sign, absence of fever in early stages, and particularly chronicity, are features of differential value, although in individual instances cases of erythema multiforme exudativum also exhibit these features. At times, chickenpox and generalized vaccinia have been confused with this condition.[15b]

As a result of idiosyncrasy or hypersensitivity to a variety of drugs, a clinical condition of the skin and mucous membranes closely resembling, if not identical with, erythema multiforme exudativum may result.

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17. Murphy, R. C.: An Eruptive Fever Involving the Mouth and Eyes (Stevens-Johnson's Disease): Report of a Case, New England J. Med. **230**:69-71, 1944.

18. (*a*) Fletcher and Harris.[18b] (*b*) Smith, C. A.: Unusual Case of Erythema Multiforme, Tr. Univ. Mich. Pediat. & Infect. Dis. Soc., 1929, pp. 63-67.

19. Edgar and Syverton.[12a] Fletcher and Harris.[15b]

20. Hanke, V.: Der Herpes iris des Auges, Arch. f. Ophth. **52**:263-284, 1901.

21. (*a*) Fletcher and Harris.[15b] (*b*) Smith.[18b] (*c*) Hanke.[20] (*d*) Welander, E.: Ein Fall von Erythema multiforma exsudativum mit tötlichem Ausgang, Arch. f. Dermat. u. Syph. **77**:289-296, 1905. (*e*) Corlett, W. T.: Erythema Exudativum Multiforme: Its Present Significance, with Report of a Case of Erythema Circinatum Bullosum et Haemorrhagicum, Following a Gunshot Wound, Apparently Due to Streptococcus Infection and Terminating Fatally, J. Cutan. Dis. **26**:7-14, 1908.

Among the drugs known to produce such reactions are phenobarbital,[22] phenylethylhydantoin (nirvanol),[22] diphenylhydantoin sodium,[23] phenolthalein,[24] sulfathiazole[25] and sulfadiazine.[26] A careful history of medication preceding illness is essential in differential diagnosis. Sulfonamide compounds may be administered during the prodromal stages of erythema multiforme exudativum and thus be held responsible for the subsequent eruption.[4c] In 1 of the cases in the present series (case 5) sulfadiazine was administered for four days and discontinued the day before the stomatitis appeared.

The clinical resemblance between erythema multiforme and the human form of foot and mouth disease has been pointed out.[4b] Unfortunately, knowledge of the human manifestations of the latter disease is scanty. Toward the close of the nineteenth century large numbers of cases of this disease among human beings were reported, particularly in Continental Europe. Since modern knowledge of the virus causation of the disease became available[27] there have been few authentic reports of the occurrence of cases among human beings.[28] The course of these acceptable cases was short in duration and characterized by little or no fever and the appearance of vesicles in the mouth, on the lips and on the hands, particularly about the finger tips.[28b] Thus, the authenticity of cases in which there were generalized eruptions, a high temperature, long duration and extensive involvement of the conjunctivas, the pharynx, the urethra and the anus is open to serious question.[29]

Among diseases producing stomatitis which may be confused with erythema multiforme exudativum may be mentioned herpetic gingi-

22. Ellis, F. A.: Reactions to Nirvanol, Phenytoin Sodium, and Phenobarbital: Report of a Case of Ectodermosis Erosiva Pluriorificialis Following the Ingestion of Phenytoin Sodium, South. M. J. **36**:575-579, 1943.

23. Ellis.[22] Ritchie, E. B., and Kolb, W.: Reaction to Sodium Diphenyl Hydantoinate (Dilantin Sodium): Hemorrhagic Erythema Multiforme Terminating Fatally, Arch. Dermat. & Syph. **46**:856-859 (Dec.) 1942.

24. Newman, B. A.: Phenolphthalein Intoxication, J. A. M. A. **101**:761-764 (Sept. 2) 1933.

25. Franks, A. G., and Traub, E. F.: Varioliform Eruption from Sulfathiazole, Arch. Dermat. & Syph. **46**:737-738 (Nov.) 1942.

26. Raffetto, J. F., and Nichols, S.: A Nearly Fatal Reaction to Sulfadiazine in a Ten Year Old Girl, Involving Skin, Eyes and Oropharynx, J. Pediat. **20**:753-755, 1942. Greenberg, S. I., and Messer, A. L.: Fatal Bullous Dermatitis Following Administration of Sulfadiazine, J. A. M. A. **122**:944 (July 31) 1943.

27. Waldmann, O., and Jape, J.: Die künstliche Uebertragung der Maul- und Klauenseuche auf das Meerschweinchen, Berl. tierärztl. Wchnschr. **36**:519, 1920.

28. Dlugosz, H.: Foot-and-Mouth Disease in Man, Brit. M. J. **1**:189-190, 1943. (*b*) Bojlén, K.: Foot-and-Mouth Disease in Man, Ugesk. f. laeger **103**:497-506, 1941.

29. Bojlén.[28b] Arkwright, J. A.: Foot-and-Mouth Disease in Man, Lancet **1**:1191, 1928.

vostomatitis and Vincent's stomatitis. Neither of these conditions is associated with a generalized eruption of the skin and the mucous membrane. Primary herpetic stomatitis is a disease chiefly affecting young children and characterized by fever, irritability, oral fetor, soreness of the mouth and regional lymphadenopathy. The lesions are situated chiefly in the gums, which are red and swollen and bleed easily.[30] Lesions may involve any part of the oral mucosa and, in some cases, the tonsils and pharynx.[31] Early in the course of the disease small pinhead size vesicles may be seen; these soon rupture, leaving round or irregular ovoid superficial ulcers. Herpes virus can be recovered readily by appropriate laboratory tests.[30]

Vincent's infection is not characterized by an initial vesicular stage. Cases of typical erythema multiforme exudativum have been reported as oral Vincent's infections associated with erythema multiforme of the skin and the eyes; in such instances the description of the oral lesions was not characteristic of Vincent's disease, and the diagnosis rested merely on the presence of fusospirochetal organisms in smears.[32]

MORTALITY

Erythema multiforme exudativum was originally described as a benign disease. The ordinary erythematomacular variety is rarely, if ever, fatal. The vesiculobullous type, and particularly those cases in which there is primary involvement of the mucous membrane, may be extremely severe. Although Lever [4c] was able to find only 4 fatal cases in the literature, it is believed that fatalities are commoner than their reported incidence.

Markham,[33] in describing a fatal case of "atypical virus pneumonia" on which were superimposed a severe conjunctivitis, membranous stomatitis, bullous cutaneous eruption and balanitis, stated that of 5 similar cases, 4 were fatal. The occurrence of 5 cases of erythema multiforme bullosum in a total of 28 cases observed over a thirteen year period has also been reported.[15b]

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30. Dodd, K.; Buddingh, J., and Johnston, L.: Herpetic Stomatitis, Am. J. Dis. Child. **58**:907 (Oct.) 1939. Scott, T. F. M.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis, J. A. M. A. **117**:999-1005 (Sept. 20) 1941. Ziskin, D. E., and Holden, M.: Acute Herpetic Gingivostomatitis: Report of Fifteen Cases, J. Am. Dent. A. **30**:1697-1705, 1943.

31. Long, P. H.: Herpetic Pharyngitis and Stomatitis: Report of Three Cases, J. Clin. Investigation **12**:1119-1125, 1933.

32. Chick, F. E., and Witzberger, C. M.: Erythema Multiforme Exsudativum Accompanying Oral Vincent's Infection, Am. J. Dis. Child. **55**:573-578 (March) 1938. Morrison, J. P.: A Case of Vincent's Infection Associated with Erythema Multiforme, J. Am. Dent. A. **28**:1938-1940, 1941.

33. Markham, J. D., in the Clinical Meeting of the Kingston Garrison Medical Society, J. Canad. M. Serv. **1**:471, 1944.

CAUSATION

The cause of the disease is unknown. The results of bacteriologic studies were inconclusive. Blood cultures have uniformly failed to yield bacterial growth.[34] Cultures of the involved eyes have either been sterile or yielded growth of normal flora, such as Staphylococcus albus or Streptococcus viridans.[15b] Streptococci have been recovered rather frequently from cultures from the mouth and throat, and some authors have been impressed by the possible causal significance of this finding.[10] It is apparent, however, that the organisms isolated were not always beta hemolytic streptococci.[10] Kove [14c] found hemolytic streptococci in throat cultures from both of his cases. However, in another series, these organisms were recovered from throat cultures in only 3 of 14 cases.[15b] Moreover, in another case beta hemolytic streptococci were present in the throat during the first attack of the disease but were not found in a recurrence six months later.[12a] In 1 fatal case streptococci may have played a role, since they were recovered in pure culture from bullae.[21e] In contrast, most of the bullae cultured by other observers have been sterile.[35] It is apparent, therefore, that hemolytic streptococci are not found with enough consistency in the majority of cases to suggest their causal relationship to the disease. In occasional instances, they may play a contributory or secondary role. Case 3 of the present series is an example of this. Aside from the streptococcus no organism has been incriminated as a causative agent of the disease. Fusospirochetal organisms have been present in some cases [32] and absent in others.[36]

Only two reports were encountered in which inoculations in animals were undertaken. Vesicular fluid from 1 patient was inoculated in mice, rabbits and guinea pigs; in each instance the intracerebral, intraperitoneal and intradermal (foot pad) route was used.[12a] In another case, guinea pigs were inoculated in the foot pads with vesicular fluid.[14a] The negative results obtained in both of these studies offered presumptive evidence excluding the presence of the viruses of herpes simplex and foot and mouth disease.

The following cases were observed on the medical wards of the Regional Station Hospital at Fort Bragg, N. C. The management of the cases was determined by the medical officers in charge.

REPORT OF CASES

CASE 1 (fig. 1).—An 18 year old white soldier with two months of Army service was hospitalized on May 5, 1943, complaining of photophobia and itching of the eyes, sore mouth and throat and cough.

34. Fletcher and Harris.[15b] Murphy.[17]

35. Kove.[14c] Fletcher and Harris.[15b] Murphy.[17]

36. Edgar and Syverton.[12a] Kove.[14c] Rosenberg and Rosenberg.[16d]

The illness began on April 28 with malaise, which improved the next day. On April 30 he awoke with a cough which was at first dry; after a few days it became moderately productive and was associated with headache. The day before hospitalization his eyes began to itch, and photophobia developed. The next day the mouth and the throat became sore. No history of ingestion of drugs could be elicited. Of possible significance was a history of "trench mouth" several years previously.

At the time of admission the patient appeared moderately ill and extremely uncomfortable. The buccal mucosa and the pharyngeal walls were coated with thin white "slimy" exudate. On the hard palate were a few whitish irregular patches, each somewhat less than 1 cm. in diameter. The lips were swollen, and on the lower lip were several small vesicles. The patient could scarcely open his eyes because of photophobia, and yellowish exudate appeared between the closed lids. Both the palpebral and the bulbar conjunctivas were edematous and diffusely

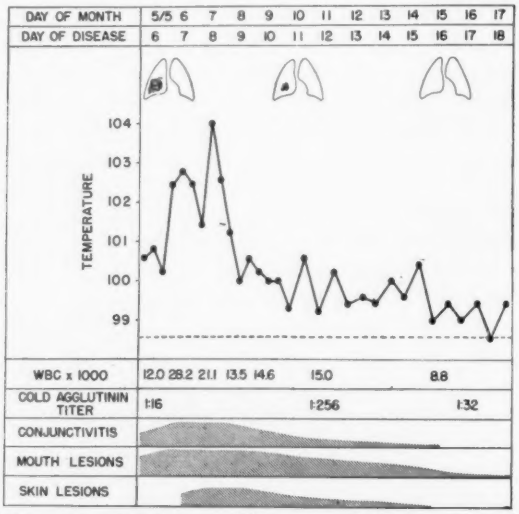

Fig. 1 (case 1).—Erythema multiforme exudativum and pneumonia.

injected. The submaxillary lymph nodes were enlarged and tender. At the base of the right lung posteriorly moderate dulness and numerous fine rales were elicited. The remainder of the physical examination revealed no abnormality.

The temperature rose to a maximum of 104 F. on the third hospital day, and thereafter low grade fever persisted for a week. The course was one of progressive involvement of the mucous membranes of the lips, the mouth, the pharynx and the eyes for four days followed by slow healing of the lesions. At the height of the reaction the buccal and pharyngeal mucosa, the tongue and the nasal mucosa were covered with a "slimy" white pseudomembrane, which was not unusually foul smelling. Successive crops of vesicles appeared on the lips, and in a few hours they became macerated and took on the appearance of the whitish patches in the mouth.

On the day after the patient's admission crops of deep-seated, "shotty" grayish vesicles, surrounded by an erythematous halo, appeared on the palms; they persisted for more than a week. No other areas of the skin were involved.

By the tenth day of disease involution of all lesions was evident, and the subjective complaints referable to the eyes and the mouth lessened. Rales in the right lung were audible until the twentieth day of illness. The total duration of hospitalization was six weeks, but eventual full restoration to normal health resulted. Treatment was palliative and symptomatic, consisting of sedatives, hydrogen peroxide and sodium perborate mouth washes; later sulfathiazole pastes, and boric compresses to the eyes were used.

Pertinent laboratory data are indicated in figure 1. The roentgenogram of the chest taken on admission showed rather extensive nonlobar infiltration, of a feathery character, in the lower lobe of the right lung which resolved and disappeared in the course of two weeks (fig. 2). Despite the leukocytosis during the febrile period, the differential formula was normal except for 8 per cent eosinophils at the time of admission. In subsequent differential counts the eosinophils were not above 4 per cent. Numerous analyses showed the urine to be

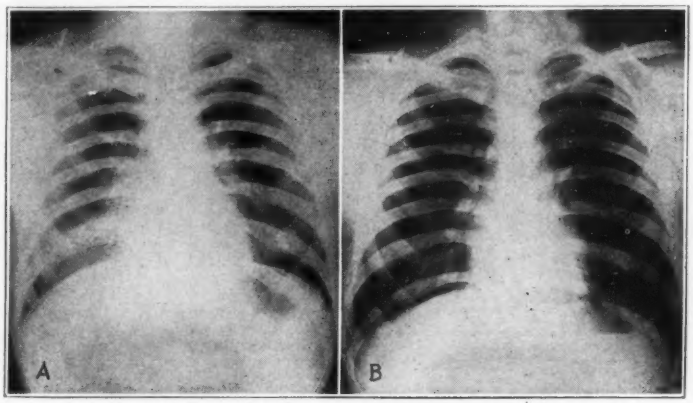

Fig. 2 (case 1).—*A*, sixth day of illness; pneumonic infiltration, lower lobe of right lung. *B*, twenty-second day of illness; lung fields clear.

normal except for slight albuminuria. The Kahn reaction was reported as doubtfully positive on the ninth day of illness and negative on the twelfth day.

Numerous cultures of material taken from the mouth and the pharynx at intervals during the course of the illness and incubated aerobically showed only a few colonies of Hemophilus influenzae and Hemophilus hæmolyticus. Conjunctival cultures were sterile. A blood culture obtained at the height of fever was sterile. Cold hemagglutinins developed in maximum titer of 1 to 256 on the twelfth day of illness.[37] Antistreptolysin titers on acute and convalescent phase serums gave no indication of hemolytic streptococcus infection.

CASE 2 (fig. 3).—A 22 year old white soldier with two months of service was admitted to the hospital on Dec. 5, 1942, complaining of sore throat.

37. Commission on Acute Respiratory Diseases: Cold Hemagglutinins in Primary Atypical Pneumonia and Other Respiratory Infections, Am. J. M. Sc. **208**: 742-750, 1944.

The illness began on December 2 with sore throat, cough, malaise, chilliness and feverishness. There was no history of recent ingestion of drugs, and the past history seemed irrelevant.

At the time of admission the patient appeared to be only mildly ill. The only abnormal physical finding was a moderate degree of pharyngeal injection, and an initial diagnosis of "nasopharyngitis" was made.

During the first four hospital days the patient made no complaints, but had a low grade fever, with a temperature which was not above 100.6 F. On December 9 he began to complain of a sore mouth, accounted for by the finding of several bullae on the floor of the mouth under the tongue. The cervical lymph nodes were not enlarged or tender. At this time the temperature rose to 102 F., and although the lungs were clear on physical examination a roentgenogram showed a moderate amount of soft infiltration in the lower lobes of both right and left lungs. For the next five days the temperature was persistently elevated

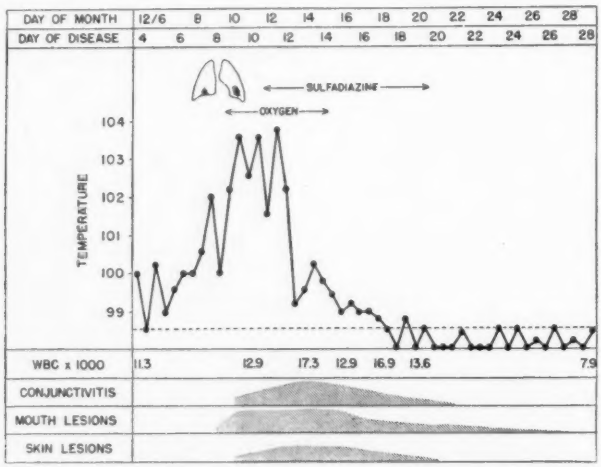

Fig. 3 (case 2).—Erythema multiforme exudativum and pneumonia.

between 102 and 104 F. The patient became somewhat dyspneic and slightly cyanotic on the lips and nail beds and was placed in an oxygen tent. Rales over both lung bases and moderate dulness over the base of the right lung posteriorly were first detected on December 12. The lesions in the mouth, first noted on December 9, spread rapidly, and the buccal and gingival mucosa, the soft palate and the pharynx were covered with a patchy, grayish membrane, and the mucosa itself became fiery red. Despite the extensiveness of the exudate it was not especially malodorous. On December 10 the conjunctivas of both eyes became diffusely injected. On the same day the patient complained of dysuria, and an excoriated area covered with seropurulent exudate was seen at the tip of the urethral meatus. For a week the patient was miserable because of profuse salivation, extreme difficulty in swallowing and speaking, cough and dysuria, but by the sixteenth day of illness the oral and penile lesions had begun to heal, the temperature was nearly normal and the respiratory distress had disappeared. Convalescence proceeded uneventfully, and complete recovery followed.

Treatment was symptomatic except for the administration of sulfadiazine from December 12 to December 20. The temperature fell toward normal shortly after chemotherapy was begun, but it is not clear whether this result was coincidental or due to therapy.

Slight leukocytosis with normal differential leukocyte counts was found during the first week of illness. At the end of the febrile period there was more definite elevation of the total leukocyte count associated with an increase in polymorphonuclear leukocytes to 87 per cent. The urine was normal throughout the illness. Stained smears from the mouth and the throat revealed only a small number of fusiform bacilli and spirochetes. Aerobic cultures of the throat and the sputum revealed only normal flora. Staphylococcus albus was cultured from the urethral lesion. A blood culture obtained at the height of fever on December 11 was

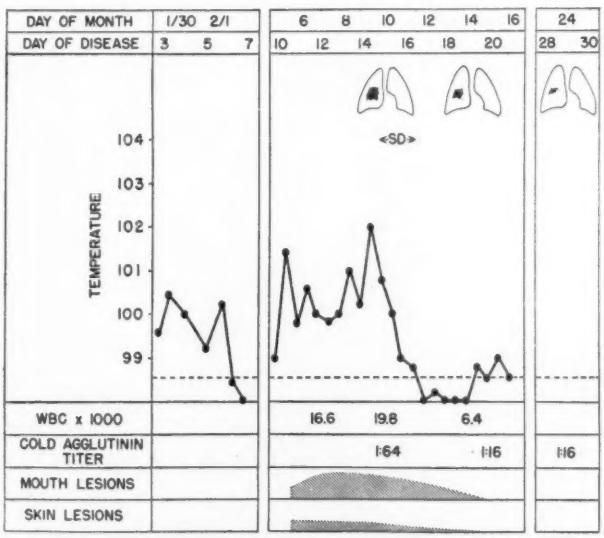

Fig. 4 (case 3).—Erythema multiforme exudativum and pneumonia; concurrent hemolytic streptococcus infection.

sterile. Specimens of serum were not obtained, so that cold hemagglutinin and other serologic tests could not be performed.

Case 3 (fig. 4).—A 23 year old white soldier with a year and a half of miltary service was admitted to the hospital on Jan. 29, 1944, complaining of feverishness, sore throat, cough and substernal pain of two days' duration. He did not appear seriously ill. The only abnormal finding was moderate injection of the pharynx, without exudate; the remainder of the physical examination, including that of the chest, revealed no abnormality. The temperature on admission was 100.4 F., falling to normal on the fourth hospital day. With bed rest the symptoms subsided, and the patient was discharged to duty on February 2, with a diagnosis of "common cold." No laboratory studies were made. While in the hospital he received codeine and acetylsalicylic acid; there was no history of preceding medication.

On February 5 the patient was readmitted to the hospital because of a recrudescence of sore throat. Physical examination again yielded normal findings except for an injected pharynx and moderately enlarged and tender cervical lymph nodes. The next day the patient complained for the first time of soreness in the mouth and, later on the same day, of dysuria. The mucous membranes of the mouth at this time were found to be diffusely reddened with patches of whitish exudate on the buccal mucosa, the gums, the soft palate and the pharynx. At the urethral meatus was a red excoriated lesion resembling the base of a vesicle from which the top had been removed. No other cutaneous lesions appeared, nor were the conjunctivas or nasal mucosa involved. On February 10 rales were heard at the base of the right lung posteriorly. Although the patient was uncomfortable because of the soreness of the mouth, at no time did he appear acutely or seriously ill. The oral and penile lesions healed by February 14, but the cough and the abnormal physical signs in the chest persisted for another week.

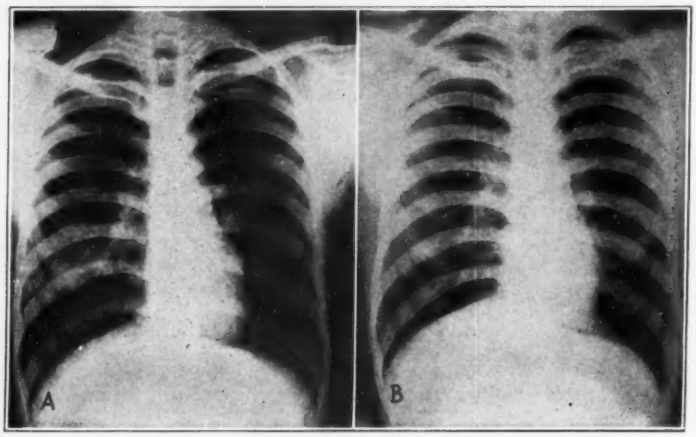

Fig. 5 (case 3).—*A*, fifteenth day of illness; pneumonic infiltration, right midlung field. *B*, thirty-fourth day of illness; lung fields clear.

Treatment was symptomatic except for the use of sulfadiazine on one day. Acetylsalicylic acid and codeine were administered throughout the hospital stay.

Roentgenograms of the chest on February 10 showed soft peribronchial infiltration in the middle lobe of the right lung (fig. 5). This lesion resolved slowly and was no longer visible in roentgenograms on February 29. The patient exhibited leukocytosis, as indicated in figure 4, but the differential leukocyte counts were normal. The urine was normal.

Cultures of material obtained from the throat on February 6, 10 and 16 and a culture of the sputum on February 19 all showed a small number of colonies of beta hemolytic streptococci of group A, type 30, without other significant bacterial organisms. Examination of smears of the mouth and the throat revealed no fusiform bacilli or spirochetes. A urethral smear showed gram-negative bacilli.

In addition to the elevated titer of cold hemagglutinins shown in figure 4, a diagnostic increase in antistreptolysin titer of 5 dilution increments was demonstrated in convalescent phase serums.

CASE 4 (fig. 6).—A 36 year old white soldier with two years of military service was admitted to the hospital on April 2, 1944, complaining of sore throat and hoarseness.

The patient was well until March 30, when he noted cough and slight pain on swallowing, both symptoms increasing in severity until admission. He denied feeling feverish or chilly but noted that his eyes were dry and irritated. There was no history of recent ingestion of drugs. Of possible significance was the patient's military occupation, which was that of butcher; his principal duty was the handling of frozen meats.

On admission the patient appeared acutely ill and in great distress because of difficulty in speaking and swallowing. The lips, the buccal mucosa, the tongue, the soft palate and the uvula, the tonsils and the pharyngeal walls were uniformly covered by a rather thick, gray-green, foul-smelling membrane. The mucosa

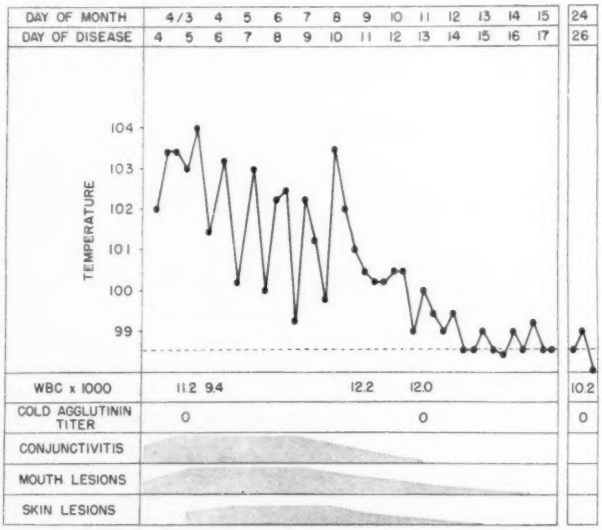

Fig. 6 (case 4).—Severe erythema multiforme exudativum without pneumonia.

underneath was deep red. The bulbar and palpebral conjunctivas were intensely red, edematous and covered with purulent exudate. There were several small conjunctival hemorrhages. On the palms and the backs of the hands and on the soles were numerous rather deep-seated unilocular firm vesicles, about 0.5 cm. in diameter, and surrounded by a narrow erythematous zone. On the under surface of the scrotum and about the meatus of the glans penis were a number of weeping excoriated lesions having the appearance of broken vesicles. The skin was elsewhere uninvolved. The lungs were clear. There was no cervical or generalized lymphadenopathy, and the remainder of the physical examination revealed no abnormality.

For a week the patient was acutely ill. He was unable to speak and could swallow only with great difficulty. It was necessary to administer fluids parenterally during this time. The temperature was irregular and swinging, varying between 99.2 and 104 F. for eight days. By the twelfth hospital day definite

improvement in the condition of the mouth and the eyes was evident, and the cutaneous lesions began to dry up. A few macular lesions subsequently appeared on the extensor surfaces of the elbows and on the soles. On a few occasions fine and coarse rales were heard in the chest. Recovery was slow but eventually complete.

Therapy was symptomatic and consisted of compresses and ointments to the eyes and cutaneous lesions and saline and sodium perborate mouth washes.

Roentgenograms of the chest on the fifth and eighth days of illness were normal. The serologic test for syphilis (Kahn) elicited a negative reaction. The total leukocyte counts were not remarkable (fig. 6), and the differential counts were normal. The urine was normal except for transient febrile albuminuria. Cultures of the conjunctivas yielded no bacterial growth. Throat cultures revealed only normal flora. Cold hemagglutinins were not present in the patient's serums, and there was no change in antistreptolysin titer during and after the illness.

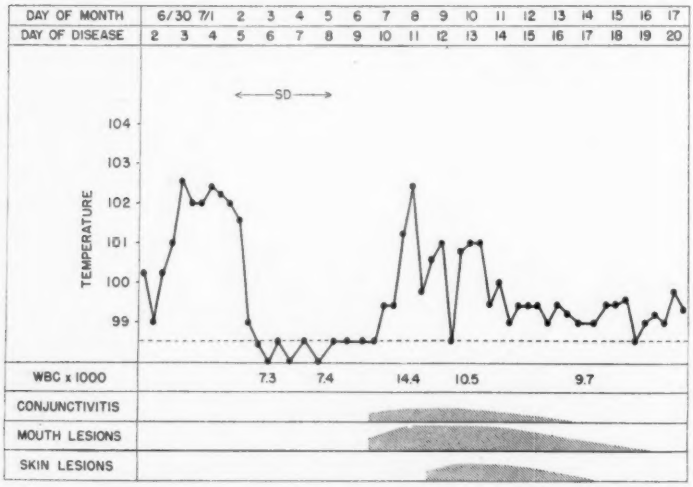

Fig. 7 (case 5).—Erythema multiforme exudativum without pneumonia.

Histologic section of a biopsy specimen taken from the margin of one of the cutaneous lesions showed no inclusion bodies and only nonspecific inflammatory changes.

CASE 5 (fig. 7).—An 18 year old white soldier with one month of military service was admitted to the hospital on June 29, 1943, complaining of sore throat. The patient was undergoing dental treatment for carious teeth, and on June 19 and 26 several teeth were extracted. On the day before hospitalization a sore throat developed, but he had no other symptoms. The past history was noncontributory. A history of recent medication was not obtained.

At the time of admission the temperature was 100.2 F., and the patient appeared only mildly ill. The only abnormal findings were moderate redness of the pharynx and many carious teeth. The day after admission the temperature rose to 102.4 F., and it remained at this level for three days. During this time there were no further abnormalities observed, although the patient still complained

of sore throat. Because of the fever, sulfadiazine was administered from July 2 to July 5, in a total dose of 18 Gm., during which time the temperature returned to normal.

On July 6 the patient first complained of a sore mouth. The next day numerous bullae, containing clear fluid, were seen on the inner borders of the lips and on the buccal mucosa. On the gums and the under surface of the tongue were whitish plaques of necrotic tissue and exudate, not easily removed, and appearing to be the remains of macerated bullae. In a few areas the mucous membrane was excoriated. Lesions were present also on the tonsils, the pharyngeal wall and the tip of the uvula. There was no cervical lymphadenopathy. The conjunctivas were injected but contained no exudate.

In the course of the next three days new bullae continued to appear, and the condition of the mouth grew worse. Confluent thin grayish white membranes covered most of the buccal, gingival and palatal mucosa. Swallowing became difficult and painful. On July 9 several maculopapular lesions, somewhat viola-

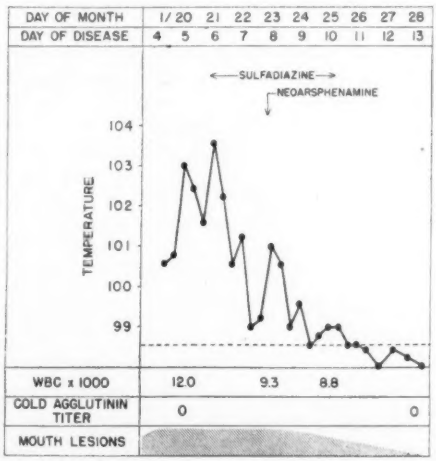

Fig. 8 (case 6).—Erythema multiforme exudativum confined to the mucous membranes of the mouth.

ceous, were found grouped about the urethral meatus; they soon became ulcerated and crusted. During this time there was a second febrile period lasting four days. By July 14 improvement in the condition of the mouth was evident, and at this time the penile lesions were healed and the conjunctivitis had subsided. The lesions in the mouth were treated with saline gargles, hydrogen peroxide and gentian violet medicinal. The patient was returned to duty on July 24, fully recovered.

A series of roentgenograms of the chest taken on June 29 and July 2, 7 and 12 all were normal. Total and differential leukocyte counts were normal throughout the illness except for one observation during the second febrile period. The urine was normal. Cultures of material from the throat revealed only normal flora. Serologic studies were not made.

CASE 6 (fig. 8).—A 22 year old white soldier with one year of military service was admitted to the hospital on Jan. 19, 1943, because of a sore throat. Nine

days before admission he complained of feverishness, chilliness, malaise, cough and sore throat and was confined to quarters for several days. These symptoms subsided, and he returned to duty. Three days before admission hoarseness developed, his mouth became sore, and swallowing became painful.

The patient was only mildly ill but extremely uncomfortable because of the condition of his mouth, which showed a pronounced generalized stomatitis and gingivitis with numerous vesicular lesions on the buccal and palatal mucosa, some of which were hemorrhagic. In addition there were many plaques of grayish exudate on the gums, the angles of the lips and the buccal and palatal mucosa. The posterior pharynx was not severely involved, and indirect visualization revealed only redness of the supraglottic structures and the vocal cords. The cervical lymph nodes were enlarged but not tender. There were no conjunctival or cutaneous lesions. The lungs were clear, and the remainder of the physical examination revealed no abnormality.

The maximum temperature was 103.6 F., and a temperature of 100 F. or more persisted for five days in the hospital. The oral lesions improved slowly over the course of ten days. Sulfadiazine, neoarsphenamine and local applications of sodium perborate were used in treatment, without obvious effect.

Roentgenograms of the chest on January 20 and 25 were normal. The leukocyte count was moderately elevated on admission but normal thereafter, and the differential leukocyte counts were normal throughout. The Kahn reaction was negative. Urinalysis yielded only normal findings. Three aerobic cultures of material from the mouth and throat revealed only normal flora (alpha streptococci, Hemophilus influenzae, and Staphylococcus aureus). On one stained smear of the oral lesions "many" fusiform bacilli were seen; on another, no fusiform bacilli or spirochetes. A blood culture remained sterile.

ETIOLOGIC STUDIES

An attempt was made to transmit an infectious agent to various animal species using blood, throat washings, vesicle fluid and other materials obtained from some of the patients included in this report. Although these studies were extensive in nature, employing a variety of animals as well as embryonated hens' eggs, the results were negative. Nevertheless, because there have been so few reported studies of this kind in cases of erythema multiforme exudativum it is believed worth while to describe the procedures in some detail.

Material from 4 of the cases was available for inoculation in animals and eggs. In addition, lung from a fatal case, obtained in the frozen state, was tested for infectivity.[38]

In each instance material for inoculation was obtained at the height of the disease. The procedures were carried out immediately after the

38. The patient died three days after admission to the hospital, exhibiting signs of pneumonia and widespread vesicular lesions of the skin and the mucous membrane, typical of the severe form of erythema multiforme exudativum. Portions of lung were sent to this laboratory through the action of Major C. T. Nelson, Medical Corps, Army of the United States, of the Fourth Service Command Laboratory and Lieut. Col. T. C. Goodwin, Medical Corps, Army of the United States, and Capt. Parker Beamer, Medical Corps, Army of the United States, the Station Hospital, Fort McPherson, Ga.

Summary of Attempts to Isolate an Agent in Animals and Eggs from Cases of Erythema Multiforme Exudativum *

Case No.	Material		Animal	Number	Initial Passage: Route	Initial Passage: Observation, Days	Subsequent Passages: Animals per Passage, Number	Subsequent Passages: Interval, Days	Subsequent Passages: Inoculum	Subsequent Passages: Route	Histologic Sections Examined
1	Vesicular fluid	Unfiltered	Mice	2	I.c.	13	2	10	Brain	I.n.	
							2	10	Lung	I.n.	
	Exudate, eyes	Unfiltered	Mice	6	I.c.	13	2	10	Brain	I.n.	
							3	10	Lung	I.n.	
	Exudate, palate	Unfiltered	Mice	3	I.p.	20	1	9	Liver and spleen	I.n.	
							2	10	Lung	I.n.	
	Sputum	Unfiltered	Mice	6	I.n.	10	3	10	Lung	I.n.	
				6	I.n.	20	1	10	Liver and spleen	I.n.	
							2	10	Lung	I.n.	
	Blood, defibrinated	Unfiltered	Mice	4	I.p.	20	1	10	Liver and spleen	I.n.	
							2	10	Lung	I.n.	
4	Throat washings	Unfiltered and filtered	Rabbit	1	Cornea	5	..	..	.....	.....	Yes
				1	Eye, ant. chamber	23					
				2	I.c.	23					
				1	I.d.	23					
			Guinea pig	2	I.d. and foot pad	23					
		Unfiltered	Egg	6	CHA	1-4	..	..	.....	.....	Yes
		Filtered †	Egg	12	CHA	1-4	1	15	CHA	CHA	Yes
	Vesicular fluid and blood, defibrinated	Unfiltered	Rabbit	1	Cornea	3	1	1	Cornea	Cornea	Yes
			Monkey, rhesus	1	Penis, cornea, i.d.	21	1	1	10	Skin of penis	Penis	Yes
	Vesicular fluid	Unfiltered †	Rabbit	1	I.d., penis	21					
			Egg	3	Amniotic	3	2	4-8	4	Embryo and amniotic fluid	Amniotic	Yes
				3	I.c.	3	1	4	4	Brain	I.c.	Yes
				3	Eye	3-4	1	4	4	Eye	Eye	Yes
	Blood, defibrinated	Unfiltered	Rabbit	1	I.d. and penis	4	..	..	..	.....	.....	Yes
			Mice	6	I.c.	4-21	2	6-8	4	Brain	I.c.	Yes
			Hamster	4	I.c.	21						
			Cotton rat	4	I.c.	21						
		Filtered †	Egg	3	CHA	3	2	4-8	4	CHA	CHA	Yes
				3	Amniotic	4	2	4-8	3	Amniotic fluid	Amniotic	Yes
				3	I.c.	4	1	4	3	Brain	I.c.	Yes
				3	Eye	4	..	..	..	.....	.....	Yes
5	Vesicular fluid	Unfiltered	Rabbit	2	Cornea	21						
			Mice	10	I.c.	21						
				8	I.n.	21						
6	Vesicular fluid	Unfiltered	Cotton rat	2	I.n.	7-28						
			Mice	6	I.n.	7	3	4-6	7-10	Lung	I.n.	
				6	I.c.	3-28	1	4	3	Brain	I.c.	
Fatal case	Lung	Unfiltered	Rabbit	1	Cornea	7	..	..	..	.....	.....	Yes
				1	I.d. and penis	14						
				1	I.c.	14						
			Guinea pig	2	I.d. and foot pad	14						
			Monkey, rhesus	3	I.d. and penis	14						
			Mice	8	I.c.	14						
			Hamster	3	I.c.	14						
		Filtered †	Egg	6	CHA	3	3	6-8	3	CHA	CHA	Yes
				6	Amniotic	3	3	6-7	3	Amniotic fluid	Amniotic	
				7	Yolk sac	5	1	6	5	Yolk sac	Yolk sac	Yes

* The expansions of abbreviations used are as follows: i.d., intradermal; i.c., intracerebral; i.n., intranasal; i.p., intraperitoneal; CHA, chorioallantoic membrane.

† This material was sterile for bacteria.

materials were obtained (cases 1, 5 and 6) or else the materials were stored in a cold box (solid carbon dioxide) in sealed glass containers for variable periods until used (case 4, fatal case). The studies carried out on material from each case are recorded in summary form in the table.

The results were uniformly negative. In 1 monkey a few tiny vesicles developed on the penis a week after inoculation on the skin of the penis with material from case 4. However, the involved skin was passed to another monkey in which lesions did not develop. Moreover, lesions were not observed in 3 other monkeys inoculated on the penis with lung suspension from the fatal case.

With all material employed and by all routes of inoculation some deaths of embryonated eggs occurred at irregular intervals after inoculation. Some of these deaths were due to trauma and others to bacterial contamination. Numerous histologic sections were examined after staining with hematoxylin and eosin and with Giemsa stain. In no instance were inclusion bodies or other specific lesions recognized.

COMMENT

The chief features of interest in these 6 cases of erythema multiforme exudativum was the occurrence of pneumonia in 3 of them. Lesions in the respiratory tract have been described by previous authors, but their prominence as an essential feature of the disease has not been emphasized. The pharynx, epiglottis, vocal cords and trachea are not infrequently involved by the process which so prominently involves the mucous membranes of the oropharynx. In a fatal case [21d] there was ulceration of the epiglottis, the vocal cords were denuded, and the tracheal mucosa showed small ulcerations with the hemorrhage. Another case, at autopsy, showed "acute diphtheritic pharyngitis" and an "area of diphtheritic ulceration" on the larynx.[18b]

Involvement of the bronchi and the pulmonary parenchyma is not uncommon. Pneumonia was present in 3 of 16 cases in one series.[15b] Markham [22] mentioned 5 cases in which there were "atypical virus pneumonia" and lesions of the skin, mouth, eye and penis. In 2 of 3 cases of "atypical" ulceromembranous stomatitis reported by Henry,[10] there was clinical and roentgenographic evidence of pneumonia. Finland observed a number of cases with pneumonia, 3 of which were fatal.[39] Several others have also reported cases with physical signs and roentgenographic evidence of pneumonia.[40]

In 1 of the cases of Stevens and Johnson the diagnosis "bronchopneumonia" was made by physical examination.[8] Another patient had

39. Finland, M.: Personal communication to the author.

40. Lever.[4e] Haddad.[11] Erger, B. D.: Erythema Multiforme Pluriorificialis (Stevens-Johnson Disease), Mil. Surgeon **95**:308-312, 1944.

rales, but a roentgenogram of the chest was not taken.[14a] In the majority of reported cases the lungs were either not mentioned at all or were described as clear on physical examination but roentgenograms of the chest were not reported.

On the basis of the present series, and from a consideration of the previously reported cases, it seems probable that pneumonia occurs more often in this disease than has been recognized hitherto. The situation appears to be somewhat analogous to that of primary atypical pneumonia; in both conditions the physical signs are not those of consolidation and the rales that are detected are readily discounted and ascribed to "bronchitis." It is now well accepted that instances of mild primary atypical pneumonia can be recognized only by roentgenograms in a considerable percentage of cases. It appears probable that a similar difficulty attends the diagnosis of the pneumonia associated with erythema multiforme exudativum.

There is little available information on the pathologic nature of this pneumonia. Four cases have been reported in which pneumonia was found at autopsy. In 1 case, in which death occurred five weeks after onset. autopsy disclosed "partly suppurative, lobular, pneumonia."[20] In another case, in which death occurred more than a month after onset, and at a time when the cutaneous and oral lesions were practically healed, there was denudation of the larynx and there was ulceration of the epiglottis, trachea and both main bronchi. The lungs themselves were hyperemic and contained bluish black, nonaerated areas.[21d] In a third case, death occurred a week after onset; autopsy disclosed "severe diffuse purulent bronchitis and bronchopneumonia." It was also noted that there were "many colonies of streptococci on the lumen" of the bronchi.[18b]

In a 9 year old girl who died six days after onset, the larynx, trachea and bronchi showed congestion and the lungs were heavy and atelectatic with areas suggestive of early pneumonia. Severe atelectasis was seen throughout both lungs. Areas of pronounced pulmonary edema with escape of blood into the alveolar lumen and collections of polynuclear cells in some alveoli were noted. The bronchial walls and the alveolar and pleural capillaries were congested.[15b]

None of these reports included a detailed description of the appearance of microscopic sections of the lungs.

A reasonable suggestion as to the pathogenesis of the bronchopulmonary involvement in this disease must take into account the likelihood that the lesions in the respiratory tract are similar to those on the visible mucous membranes. The available descriptions, quoted herein, support this suggestion. In this connection, the report of Poole and

Wehger [41] on the pulmonary pathologic changes associated with exfoliative dermatitis is of possible relevance. These authors reviewed the observations at autopsy in cases of exfoliative dermatitis and regularly found desquamation of the epithelium of the trachea, bronchi, bronchioles and alveoli. They concluded that death was not due to pneumonia but to obstruction of the respiratory passages, causing suffocation.

The pneumonia of erythema multiforme exudativum may be of a similar nature, since it is altogether likely that the mucosa of the tracheobronchial tree is involved to greater or less degree by a vesiculobullous eruption identical with that seen in the mouth. However, the clinical observations in the present group of cases do not entirely support this theory of the pathogenesis of the pulmonary lesion. In case 1 the pneumonia probably antedated the visible eruption, and in case 2 it clearly preceded the eruption on the skin and mucous membranes. In exfoliative dermatitis; on the contrary, the signs of pulmonary involvement appeared late in the illness. Moreover, in the present series of cases there appeared to be no relationship between the occurrence of pneumonia and the severity of the lesions of the skin and the mucous membrane. In case 3, in which there was pneumonia, the illness was otherwise the mildest in the series from the point of view of the height of fever and the extent of involvement of the mucous membranes. On the other hand, the disease in case 4 was the severest in the group, in terms of fever and the extensive involvement of the mouth and eyes. Clinically, in this case, the larynx was severely affected and there was some evidence of bronchitis, but pneumonia was not demonstrable either clinically or by roentgenogram.

Further evidence against the suggestion of obstruction of the respiratory passages resulting from denudation of the epithelium was the absence of signs or symptoms of respiratory distress in the cases in this series. Only one patient (case 2) had moderate dyspnea and slight cyanosis. In none of the cases was there clinical or roentgenographic evidence of atelectasis. Likewise, in previously reported cases, including those with rales, and those with clinical and roentgenographic signs of pneumonia, indications of respiratory embarrassment were rarely mentioned.

Many of the features of the pneumonia in the present series of cases bore a close resemblence to primary atypical pneumonia. The prodromal symptoms, absence of physical signs of consolidation, the character of the radiographic lesion, the minimal degree of respiratory distress, the absence of pleural pain or bloody sputum and the relatively normal leukocyte count were features not unlike those commonly encountered

41. Poole, A. K., and Wehger, R. T.: Fatalities in Exfoliative Dermatitis, J. A. M. A. **102**:745-751 (March 10) 1934.

in primary atypical pneumonia. In 2 of the 3 cases with pneumonia tests for cold hemagglutinins were made, and in both a significant titer was found. In the 3 cases without pneumonia, the test was performed in 2 and in both the result was negative. With present knowledge, it would be unwarranted to regard this test as specific or diagnostic for primary atypical pneumonia. The clinical and roentgenographic observations in the cases reported, however, suggested a resemblance between the pneumonia associated with erythema multiforme exudativum and primary atypical pneumonia.

Bacteriologic studies in the majority of reported cases have not yielded results suggestive of a causal relationship. This was true also in the present series. In case 3, however, bacteriologic and serologic evidence of beta hemolytic streptococcus infection was secured. While it is improbable that this organism represents the usual cause of the clinical picture of erythema multiforme exudativum, it is possible that it may be one of the causes. In the present case, however, it is believed that the patient had a concurrent infection with hemolytic streptococcus. Other examples of what was thought to be concurrent infection with two agents of respiratory disease have been presented elsewhere.[42]

The studies carried out in animals and embryonated eggs were probably adequate to rule out the presence of the viruses of herpes simplex, vesicular stomatitis and members of the psittacosis-meningopneumonitis group in the materials tested. No etiologic agent was found. These studies neither rule out nor support a possible virus causation for cases of erythema multiforme exudativum.

SUMMARY

The severe form of erythema multiforme exudativum, with predominent involvement of the mucous membranes of the mouth, eyes, and urethral meatus, is a clinical entity. Its etiology is unknown. Although it is believed to be an infectious disease, bacteriologic studies and the results of inoculations of animals have yielded negative results. Nonbacterial pneumonia occurs frequently in this condition and is believed to be an integral feature of the disease. In its clinical features, it bears a rather close resemblance to primary atypical pneumonia.

NOTE.—Since this article was submitted for publication attention has been directed to a report by J. H. Stanyon and W. P. Warner entitled "Mucosal Respiratory Syndrome," *Canad. M. A. J.* **53**: 427-434 (Nov.) 1945. This report deals with 17 cases of the severe form of erythema multiforme exudativum. An excellent clinical description of the cases is given. Of particular interest was the demonstration of nonbacterial pneumonia in 14 of the cases. There were 2 fatalities in

42. Commission on Acute Respiratory Diseases: Association of Acute Pulmonary Lesions with Infections of the Throat, to be published.

the series; a detailed description of the pathologic findings in 1 case is included. The principal abnormal findings were in the lungs, which were almost completely consolidated but which differed in their appearance from ordinary bronchopneumonia or lobar pneumonia. Microscopic study showed the inflammatory exudate in the lungs to be of an essentially mononuclear type. The authors concluded that the pneumonia was an integral feature of the syndrome and that its cause was not bacterial and was probably viral.

ADDENDUM.—Further attempts to isolate an agent from the lung in the fatal case reported here were carried out by Dr. H. W. Schoening of the Bureau of Animal Industry, United States Department of Agriculture. Horses, cows, sheep, pigs and guinea pigs were employed. Normal animals, as well as animals immune to the New Jersey and Indiana types of vesicular stomatitis virus and to the virus of ovine ecthyma, were inoculated. No lesions were produced in any of the animals inoculated nor did exposure to material from the lung in any way affect the susceptibility of the previously normal animals to the two types of vesicular stomatitis virus.

The following officers, while at Fort Bragg, helped to make this study possible: Brigadier General H. C. Coburn, Jr., Medical Corps, Surgeon, Fort Bragg; Colonel R. T. Arnest, Medical Corps, Surgeon, Fort Bragg; Colonel G. D. Chunn, Medical Corps, Commanding Officer, Regional Station Hospital; Colonel J. N. Williams, Medical Corps, Commanding Officer, Regional Station Hospital; Colonel W. B. Daniels, Medical Corps, Chief of Medical Service; Lieutenant Colonel J. M. Kinsman, Medical Corps, Chief of Medical Service; Colonel A. Blumberg, Medical Corps, Chief of Laboratory Service, and Mrs. Ann Alvey, Pathological Laboratory Technician.

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BEHAVIOR AND PSYCHOLOGIC PROBLEMS OF YOUNG DIABETIC PATIENTS

A Ten to Twenty Year Survey

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IT IS the purpose of this paper to describe the behavior and the psychologic problems of a group of diabetic patients who have been observed from childhood through adolescence and early adulthood. All these patients were under treatment for from ten to twenty years. It is well known that normal children exhibit temporary alterations in behavior in the transition from childhood and adolescence to adult life. However, these alterations are more pronounced in diabetic children because of the abnormal regimentation to which they are subjected and because of certain psychic and physical factors associated with their condition.

MATERIAL

Forty-three patients were studied, 22 females and 21 males (table 1). Thirty-four of these patients attended the outpatient department at the Mount Sinai Hospital, and 9 were private patients. The former were treated in the pediatric clinic until they reached the age of 14, when they were transferred to the clinic for adult patients. Most of the children were from poor or lower middle class homes. Many had been receiving financial aid from government or private agencies. Even in cases in which the economic status was not that of the lower income bracket, the care and special needs attendant to the maintenance of adequate diabetic treatment often brought the families into the submarginal economic group.

As soon as a diagnosis of diabetes had been made, the patient was admitted to the wards of the hospital for regulation. At that time the child and the parents were instructed in the dietary calculations, the administration of insulin and the management of the diabetes.[1] Many cooperative children, whose diabetes was easily regulated, required no further hospitalization. On the other hand, when the patients or their parents were uncooperative, the diabetes was poorly controlled and frequent readmissions because of ketosis were necessary.

All the patients in this study were 12 years of age or younger at the onset of diabetes. The youngest was 11 months old. The diabetes started during the first five years of life in 9 of the children, between 5 and 9 years in 17 of them and between 10 and 12 years in 17 of them. Twenty patients were under continual

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1. Fischer, A. E.: A Diabetic Primer for Children, New York, privately printed, 1938.

TABLE 1.—*Survey of Forty-Three Diabetic Patients*

Patient	Sex	Case	Age at Onset of Diabetes	Duration in Years	Dominant Behavior	Occupation
M. B.	F	1	3	16	Dependent	Secretary
P. B.	F	2	10	10	Introverted, slovenly	Clerk
B. B.	F	3	11	19	Aggressive, euphoric	Salesgirl
M. B.	F	4	5	13	Depressive	None
H. C.	M	5	8	12	Self reliant, independent	Clerk
S. E.	M	6	4	15	Independent	Student
N. G.	M	7	11	13	Aggressive, independent	Furrier
R. G.	M	8	11 mo.	17	Submissive	Student
I. G.	M	9	8	12	Aggressive	Student
S. G.	F	10	9	18	Self reliant, inclined to be depressed	Housewife
E. H.	F	11	12	17	Submissive, dull	Housewife
B. H.	M	12	11	16	Suggestive of bravado, euphoric	Watchmaker
E. H.	M	13	9	13	Normal	Student
G. H.	M	14	11	14	Dependent	Salesman
A. I.	M	15	10	18	Depressive	Mechanic
H. I.	M	16	10	17	Aggressively independent	Salesman
M. J.	F	17	9	16	Normal	Secretary
M. K.	F	18	11	16	Normal	Housewife
G. K.	F	19	10	13	Normal	Salesgirl
R. K.	F	20	11	13	Depressive, insecure	Secretary
D. K.	F	21	7	12	Apathetic, indifferent	Maid
J. L.	M	22	1½	18	Rebellious, indifferent	Business
S. L.	F	23	6	13	Rebellious	Student
C. L.	M	24	4	19	Dull, submissive	Clerk
A. L.	M	25	2	14	Dull	Student
E. L.	M	26	8	12	Aggressively independent	Lens grinder
S. M.	F	27	12	13	Insecure, depressed, schizoid	Stenographer
E. M.	F	28	3	16	Normal	Student
J. M.	M	29	6	18	Normal	Clerk
A. N.	M	30	11	14	Self reliant, aggressive	Truckman
M. P.	M	31	4	18	Infantile, euphoric	Butcher
E. S.	M	32	12	10	Normal	Clerk
M. S.	F	33	4	11	Resigned	Student
L. S.	M	34	7	15	Sullen, negative	Butcher
A. S.	F	35	6	15	Dull, submissive	None
S. S.	F	36	8	16	Rebellious against diabetes and society	Salesgirl
G. S.	M	37	10	15	Indifferent	Mechanic
E. S.	F	38	9	16	Dependent	Secretary
M. S.	F	39	6	12	Normal	Salesgirl
D. T.	F	40	5	13	Normal	Student
J. T.	F	41	10	12	Temperamental, unhappy	Office worker
M. T.	M	42	6	17	Normal	Machinist
J. Z.	F	43	10	15	Dull, submissive	Housewife

observation for at least ten years and 23 for from fifteen to twenty years. All were American-born children, the majority of Russian-Jewish origin and the others of Italian, Irish or Scandinavian descent.

The family and social histories were carefully investigated, and continued contacts with the family were maintained; consequently, all the significant factors which might influence development were made known to us. These contacts with our patients became so intimate that we were family advisers to many of the group, especially with respect to education, occupation and marriage. Our case records were very complete and included reports of the child's progress at school and at home. Special note was made of the metamorphosis which always takes place during adolescence.

GENERAL FACTORS INFLUENCING BEHAVIOR

The general factors which influenced the behavior of diabetic children were similar to those which operated in other chronic illnesses, such as asthma or rheumatic heart disease. These factors were concerned primarily with the reactions which were evoked in the family circle, at school or in play.

1. *The Family.*—As in all children, home environment and the relationship between the members of the family greatly influenced the diabetic child's behavior. The financial status of the home and its emotional stability were equally important influences. Most of the patients came from underprivileged families or families with low income. The financial burden of caring for a chronic illness such as diabetes imposed an unusual strain on these families. Economic insecurity and its sequelae of tension and discord in the home were shared by the children. Not infrequently, rejection of the diabetic child was voiced because its care became an unwanted burden. Such an instance was the following case.

E. L. (case 26), diabetic since the age of 8 years, was the son of divorced parents. He and his mother occupied a single room where he witnessed prostitution and intoxication. At times his mother kept him out of their "home" so that she could pursue her profession. Suicidal tendencies developed in this child. On one occasion he deliberately withheld insulin for a week, hoping to die in diabetic coma. During a period of hospitalization we were able to convince the mother of the advantage of placing him in a foster home.

Few children realized the implications of the diagnosis of diabetes. They accepted their condition passively at first, unaware of the restrictions which it might place on them later. The parents, on the other hand, were always greatly shocked. They asked first whether their child would live, and if so, for how long. When reassured, they usually asked why the affliction had occurred and how it could have been avoided. They assumed generally that the child's diet had been at fault and blamed themselves for permitting an excessive intake of carbohydrate. They inquired as to the influence of heredity, namely, what part it played in the transmission of diabetes and how it might

affect further progeny of their own and that of the diabetic child. Soon after the initial shock had worn off, the education of the parents in the care of the diabetic child began. This process tended to lessen the anxiety by permitting the parents to share in a program which aimed to restore the child's well-being. The mother usually assumed the role of dietitian. Many children learned to administer insulin themselves. Some of them were afraid or unwilling to do so; the mother or the father then performed the injecting.

There were two common parental reactions, one being an oversolicitous coddling and pampering attitude and the other one of resentment and rejection. The former usually produced a submissive, dependent type of child and the latter a belligerent character. However, sometimes the early training in diabetic management, which led understandably to an overzealous or overprotecting attitude on the part of the mother, eventually evoked rebellion on the part of the child. Such patients all too frequently were cooperative at first, but like those children who felt rejected, soon resented the restrictions placed on them. Examples of the various behavior patterns follow:

1. Oversolicitude, Producing Dependency: R. G. (case 8) was a boy whose diabetes began when he was 11 months old. The onset at so unusually early an age accounted in part for the intense anxiety and exaggerated solicitude with which he was regarded. In addition, the parents nurtured this boy with special attention because their only other child was a deaf-mute. He was sheltered to an unusual degree throughout childhood and adolescence. This patient has been the most docile and submissive of all the male diabetic persons in the group. Now 20 years old, he is beginning to display signs of independence and self reliance for the first time.

2. Rejection, Producing Resentment: H. I. (case 16) had had diabetes since he was 10 years old. His parents were unintelligent and illiterate and were unable to understand the instructions for his care. The patient had always been difficult to manage. Insulin was given irregularly, and the boy frequently would leave home at night. He was delinquent at school. He was transferred to a foster home at the age of 12 so that the diabetes could be treated more successfully and in a less disturbed atmosphere. At first he was happy, and his behavior improved remarkably. However, after a year he reverted to his previous behavior, and in spite of a change in foster homes his conduct remained unsatisfactory. On occasion he would return to his own family, even though he fought with his brother continually. At times he had a euphoric, devil-may-care attitude. At other times he felt rejected, displayed a morbid attitude and stated at 17 years of age that he would rather die than live the restricted, handicapped life of a diabetic person. His case history is completed on page 722.

3. Overprotection, Producing Rebelliousness: J. L. (case 22) became diabetic when less than 2 years old. During his early childhood he had many illnesses—pneumonia on several occasions and recurrent otitis media and mastoiditis. His diabetes was difficult to control and he was hospitalized on several occasions. The child's father had severe asthma. The mother spent most of her life caring for her husband, who frequently was unemployed, and for her diabetic child. She took the boy to school and called for him daily. She rarely permitted him

to cross a thoroughfare alone. As he grew older, he began to show resentment against her overprotection. On one occasion he was injured when he fell off a truck on which he was riding. This accident served to increase his mother's watchfulness. Recently, at the age of 20, he decided to marry. His mother's chief concern was his inability to give himself his insulin. Yet she has never permitted him to do so, fearing that he would not measure the dose correctly. The boy recently said, "What does she want to do, come along with me on my honeymoon?"

Some parents awakened their children at night, ostensibly to have them void but actually to make certain that they were not in insulin shock. What most of these parents really feared was that death might result from an unrecognized and untreated reaction to insulin. Many children passed through a period of hypoglycemia during sleep—some could not be roused in the morning. When such episodes occurred early in the course of their diabetic experience, the parents of these children became extremely fearful. As a result, many of the mothers slept in the same bed with their children so that they might detect tremors or unusual perspiration which signified the onset of a hypoglycemic reaction during the night. The potential dangers of this practice are self evident, especially when carried through adolescence.

The presence of a diabetic child among normal siblings introduced a threat to the security of both the normal and the diabetic child. The normal child usually resented the extra care and attention which the diabetic child received. On the other hand, the presence of a normal sibling, receiving the natural affection of the parents, evoked an even greater feeling of insecurity in the child who felt stigmatized by the handicap of the diabetes. Mothers found it burdensome to prepare separate meals for their children. Resentment was aroused, and the feeling of "difference" was continually accentuated when the other children were permitted to eat unlimited portions of food, especially sweets, which the diabetic child was denied.

A unique situation occurred when in one of identical twins, M. S. (case 33), diabetes developed at 4 years of age, the sister remaining unaffected. Before the onset of diabetes the twins always had eaten their meals together. After Mildred was subjected to the diabetic regimen, she refused to permit her sister, Helen, to leave her sight for fear she would receive extra food. As a compromise both children were placed on a diabetic diet, but the mother continued to offer the nondiabetic child extra food at opportune moments. This stratagem was necessary in order to maintain harmony at home. It was only after puberty that the problem of food became less acute. Only then did the diabetic girl apparently accept her dietary restrictions and become satisfied to have her sister eat with the rest of the household while she, meanwhile, preferred to eat alone rather than be restricted at the family table.

2. *School and Play Groups.*—The associations in school and at play were almost as important as those of the home in influencing the behavior of the diabetic child. Activities in school and at play introduced new forms of competition. All children are eager to hold their place among their schoolmates. This feature of childhood raised two problems for the diabetic child: 1. Could a feeling of "difference" be avoided? 2. Could the diabetic child participate in all activities? While some children did not regard diabetes as a handicap and were not embarrassed by their friends' knowledge of it, others concealed it from their playmates. For example, many children refused to take nourishment to school since it emphasized their feeling of "difference." Girls, more often than boys, found it difficult to be casual about their condition, and their friends often did not learn of the diabetes, except by chance. Such girls lived in constant dread lest the diabetes be discovered. They carefully hid their syringes, saccharin and insulin and hoped that their dietary restrictions would remain unnoticed. Nevertheless, their painstaking efforts often were thwarted. One girl lost her best friend because the latter accidentally learned of the diabetes from their teacher. This attempt at concealment was considered a breach of confidence between two close friends. Another patient became confused when her handbag was opened by a friend who found that it contained insulin and a hypodermic syringe. Another awkward situation arose at a patient's home when a visitor opened the refrigerator, found insulin on a shelf and inquired as to its purpose. Such examples illustrated the need for urging all diabetic children to be frank about their condition and to explain to their friends the reasons why they were restricted.

Even when a wholesome attitude toward diabetes existed, insecurity could not be avoided. Some children could not participate fully in all competitive sports. The caloric intake of many of these children was somewhat below that of physically active nondiabetic children of their own age, as it was not always possible to supply a diet which permitted maximum exercise and yet was compatible with good diabetic control. This was the accepted practice during the earlier period of this study. Some children could not play strenuously, go on hikes, ride bicycles and engage in other activities because they lacked the extra physical capacity. They were compelled to offer excuses, and this accentuated their feeling of "difference." The observance of religious functions, such as the Jewish Holy Days, Holy Communion, or Lent interrupted the usual insulin-diet schedule, thereby not only interfering with the medical control but also emphasizing the limitations which diabetes imposed on the child. The camp for diabetic children enabled the patients to join one another in physical activities and thus broke down the feeling of isolation by being in a homogeneous group. On the other

hand, a few children resented the stigma attached to the name "diabetic camp" and refused to attend.

3. *Adolescence and Maturity.*—The young nondiabetic child is trained to a more or less routine life largely within the confines of the home. His meals are nearly always eaten at home; his sleeping hours are regular, and his social life is simple. It is not difficult, therefore, to transform the daily routine of a nondiabetic child to the diabetic regimen. One can understand why excellent diabetic care is possible with young patients, for only after the child acquires greater contacts with the outer world does good control become increasingly difficult. The dependence of childhood often was replaced by independence during adolescence, which increased as the patient became self supporting

Most adolescents became increasingly resentful of others' awareness of their condition. They refused to have their teachers or prospective employers know of their disease, for they wished to be considered "equal" in a competitive world. This was especially true among the girls, for whom adolescence normally is a more difficult period of adjustment. When their friends discussed marriage, they were embarrassed and distressed. Many of them feared that diabetes would interfere with their chances of getting married and having children.

Some of the boys, assuming that they would be rejected for military service, sought to evade detection of the diabetes by taking large amounts of insulin prior to their induction examination. A few succeeded in passing the initial examination and were accepted, but unfortunately for them they were detected within a few days and discharged from the army (E. L., case 26). As a group they, like other outwardly healthy-looking boys, were embarrassed when questioned as to why they were not in military uniform. S. E. (case 6), who had been classified "4-F," became embroiled in a fight when accused of being a slacker.

In general, however, the influence of maturity on the diabetic patient has been favorable. With the approach of adult life the adjustments and the behavior of most patients improved. Even those patients whose outlook seemed rather hopeless during the teens fared surprisingly well when they were able to escape the sinister and retarding influence of a poor childhood environment.

SPECIFIC EFFECTS OF DIABETES ON BEHAVIOR

1. *Duration of Diabetes and Age of Onset.*—McGavin, Schultz, Peden and Bowen [2] stated that the earlier the child had diabetes the more readily he or she accepted it emotionally as part of the growing-up

2. McGavin, A. P.; Schultz, E.; Peden, G. W., and Bowen, B. D.: The Physical Growth, the Degree of Intelligence and the Personality Adjustment of a Group of Diabetic Children, New England J. Med. **223**:119 (July 25) 1940.

process, whereas those in whom it developed at a later age tended to rebel against it. Loughlin and Mosenthal,[3] on the other hand, reported that the earlier the onset of diabetes the greater was the tendency toward personality changes. An analysis of the age of onset of the diabetes and its duration for our 43 children, all of whom had it before 12 years of age, revealed no relationship between either the duration of the disease or the age of onset and the type of behavior. We could find no consistent difference in the degree of personality change between those in whom diabetes developed in early childhood (before the age of 6 years) and those in whom it developed between 6 and 12 years of age.

2. *Severity of Diabetes.*—Increasing amounts of insulin were needed in nearly all instances as the children matured. Some patients required large amounts of insulin (up to 150 units a day). These children displayed some anxiety because their dose had increased. However, there was no correlation between behavior and the severity of the diabetes as judged by the requirement of insulin.

3. *Regimentation of Diabetic Patients.*—During the 1920's and 1930's, when regular insulin was the only type available, a rigid regimen was required. Frequent daily injections of insulin and accurate weighing of food were necessary. At that time the use of a lower carbohydrate content of the diet was the prevailing practice. The early years of treatment of many of our patients were characterized by a high degree of consciousness of their diabetic condition. This sometimes led to subterfuge. Most patients refused to adhere to a weighed diet. The infractions were often minor, yet if children were not allowed sufficient variety and adequate caloric intake they would supplement the diet surreptitiously with candy or other sweets. Many patients reduced their intake of food just prior to medical examination, hoping thereby to submit a sugar-free urine. Occasionally, urine diluted with water was presented for analysis.

The importance of checking such minor infractions was obvious. Prescriptions for insulin and diet based on false reports led to a lack of correlation between the assumed and the actual diabetic condition. As a result, accurate "diabetic control" became impossible. The physican found himself unable to explain certain clinical and laboratory data, and the patient realized that the physician could be fooled. This encouraged the patient further, and if the physician was not on guard at each visit, complications such as ketosis might arise in spite of apparently careful supervision. Today the diet is more liberal; the number of injections are fewer because of longer-acting insulins, and regimentation has been minimized.

3. Loughlin, W. C., and Mosenthal, H. O.: Study of the Personalities of Children with Diabetes, Am. J. Dis. Child. **68**:13 (July) 1944.

We encouraged independence and self reliance by having the patients administer the insulin and regulate the diet themselves. In the first months of treatment the initial instructions were followed meticulously; the diet was weighed, urinalyses were made frequently and injections of insulin were given accurately. Then, after a few years the patients became careless, and the diet was estimated but not weighed. Subsequently, the urinalysis alone was used as a guide to the amount of insulin needed, little attention being paid to the type and the amount of food consumed. Finally, some patients completely disregarded their dietary prescriptions and omitted urinalyses, the dose of insulin being regulated merely by the way the patient "felt." In defense of their behavior most of the adolescent patients stated that they "felt better and stronger" when they had glycosuria and "weaker" when they were sugar free. They thought it logical therefore to eat freely and excessively, and they disregarded the glycosuria. An attitude of bravado, not peculiar to diabetic children alone but characteristic of adolescence in general, appeared in an exaggerated form at this time. Nevertheless, even careless patients rarely failed to take their daily dose of insulin.

4. *Hypoglycemia.*—We regard hypoglycemia with anxiety and do not agree with those who have a complacent attitude toward it, for the harmful effects of hypoglycemia on behavior are both immediate and delayed. Cerebral changes can be demonstrated by the electroencephalogram, which reveals abnormalities in some diabetic children not only during hypoglycemia but also for some time after the blood sugar level has risen above normal.[4] These changes may be due either to anoxia or to metabolic effects secondary to hypoglycemia.

Immediate Effects: The usual symptoms of hypoglycemia, such as pallor, sweating, dizziness and tremors, are well known. It has not been recognized generally that young children also become irritable and fretful. Failure to understand the basis of such erratic conduct of young children often started a chain of circumstances which affected future behavior patterns. These children were scolded or punished because of actions beyond their control. On the other hand, others learned to simulate the symptoms of hypoglycemia in order to obtain extra sweets or to escape from an unpleasant situation. We have also known children who frequently feigned reactions to insulin in order to avoid school, especially at examination time.

The older children and adolescents exhibited the commoner symptoms of hypoglycemia, such as confusion, negativism and violent outbursts. The occurrence of hypoglycemia in public often led to embarrassment. Some children had convulsions and became unconscious in the presence of their playmates. One patient, N. G. (case 7),

4. Strauss, H., and Fischer, A. E.: To be published.

while in a hypoglycemic state attacked a pedestrian and was placed under arrest.[5] Another boy, A. N. (case 30), undressed on the street while in a state of insulin shock. Erratic behavior sometimes occurred at school, and teachers were confused by the bizarre responses not typical of the child. Sometimes patients displayed abnormal behavior only during late afternoon hours when, after an inadequate lunch or strenuous exercise, the blood sugar fell to hypoglycemic levels.

Delayed Effects: Repeated hypoglycemic reactions over a long period may affect cerebral function, with consequent mental deterioration. This process is a slow, cumulative one which may not be demonstrable for years. Unrecognized hypoglycemic episodes may occur during sleep. Cerebral deterioration may be explained on the basis of such reactions in addition to those which occur and are recognized during the day.

There were several patients who had frequent and prolonged reactions to insulin over a period of years and who no longer displayed their original intellectual capacity.

S. E. (case 6) asserted that his memory and concentration at 20 years of age were not so acute as they had been during elementary and preparatory school years.

S. L. (case 23), 20 years old, felt chagrined because she barely passed college examinations. She stated that she was stupid, was unable to study properly and felt that she was not nearly so apt as during her earlier schooling.

The following children presented severer disturbances.

B. B. (case 3) became diabetic at 11 years of age. At that time she was a healthy happy girl of average intelligence. She deteriorated progressively until, at 29 years of age, she was euphoric and almost moronic.

M. B. (case 4), who was a child of average intelligence at the onset of the diabetes, exhibited mental deterioration and dulling of the intellect following repeated severe reactions to insulin. She was considered to have had epilepsy and died during a seizure. At autopsy the brain revealed diffuse gliosis of the cortex and subcortex, indicating degenerative encephalopathy. These findings were similar to those reported by Root and Styron.[6]

The question arises as to whether repeated episodes of hypoglycemia may precipitate underlying epilepsy or whether hypoglycemia may produce sufficient damage to cause epileptiform seizures.[7] While the significance and the treatment of reactions to insulin have been stressed repeatedly, we feel that the potential dangers from many such recurrent episodes have not been emphasized sufficiently.

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5. Adlersberg, D., and Dolger, H.: Medico-Legal Problems of Hypoglycemic Reactions in Diabetes, Ann. Int. Med. **12**:1804 (May) 1939.

6. Root, H. F., and Styron, C. W.: Insulin Hypoglycemia and Vascular Accidents in Diabetes Mellitus, J. Mt. Sinai Hosp. **8**:953 (Jan.-Feb.) 1942.

7. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes Mellitus, ed. 7, Philadelphia, Lea & Febiger, 1940, p. 498.

5. *Complications.*—Children did not worry about possible complications. Adolescents, however learned of them through reading and through contacts with older diabetic patients. The various manuals for diabetic persons have stressed the more serious complications arising in older diabetic patients and all too frequently have alarmed the young patients.

Diabetic complications affected the patients by interfering with normal life and by causing anxiety and depression. This was especially true of ocular complications, such as cataracts and retinopathy, which bear the threat of blindness. It was tragic to have survived fifteen years of childhood diabetes, to have learned a trade and then to become blind.

Furunculosis and other intercurrent minor infections which could be cared for at home did not, as a rule, change the daily routine. However, severer suppurative infections did interfere with attendance at school and at work. Hospitalization was required for any infection accompanied with ketosis and occasionally for complications of a degenerative nature.

Two patients had active pulmonary tuberculosis, G. H. (case 14) and E. L. (case 26). G. H.'s infection was arrested; he married and became self supporting, E. L. contracted tuberculosis after an unsuccessful marriage and has advancing lesions requiring institutional care.

Acne, sometimes severe, occurred in almost all the male patients during puberty. It naturally caused considerable embarrassment and added to the problems of adolescence.

Atrophy or hypertrophy of the subcutaneous fat[8] due to injections of insulin proved a disturbing factor, especially in girls. They wore long-sleeved dresses in order to conceal the deformed areas and avoided swimming because of the appearance of the thighs. The condition in some of the children seemed to improve following puberty. It was hoped that the introduction of protamine zinc insulin would reduce the incidence of tissue deformity. Unfortunately, this was not the case, for tissue reactions have continued to appear with the newer modifications of insulin.

Short stature existed in some patients and in a few led to minor behavior disturbances. Fortunately, none of our patients exhibited so-called diabetic dwarfism. Boys were more conscious of their short stature than girls. H. C. (case 5), hoping to become taller, slept with his feet tied to a weighted pulley at the foot of his bed and with another rope around his waist which pulled his trunk in the opposite direction.

8. Fischer, A. E.: The Frequency of Atrophy of the Subcutaneous Fat Following the Injection of Insulin, Am. J. Dis. Child. **38**:715 (Oct.) 1929.

6. *Development of Abnormal Behavior.*—A number of patients exhibited pronounced behavior changes over a period of years. These included bellicose acts, euphoria, wanderlust, alcoholism, fatalism, depression and suicidal trends. Fortunately, in the majority of instances these aberrations were transient. However, 2 patients displayed distinct psychopathic tendencies severe enough to warrant institutionalization. Their case histories in brief follow.

S. M. (case 27) had been diabetic since 12 years of age. Her family was constantly in dire economic straits. The father was a pushcart peddler who worked irregularly. The main support of the family came from charitable organizations and relief agencies. Although of more than average intelligence (an intelligence quotient of 112 at 19 years of age), the patient could not complete high school successfully. She was always reserved and uncommunicative. It was noted that she seemed unmoved by any scolding from either parent. At 19 she first displayed frank schizophrenic behavior by locking herself in her room for almost two weeks, talking to no one and refusing to wash herself. She directed a number of threatening letters of paranoid type to the physicians and the social workers, and she was transferred, subsequently, to a psychiatric institution.

L. S. (case 34) was the only son in a family which included four daughters. The father, a truck driver, was devoted to his family. The mother was a dull-witted but conscientious woman. Once, when confronted by her son's teacher with a report of poor grades in school, she blandly remarked that it made little difference how he fared in school inasmuch as he could not live long! The four sisters were pleasant, well adjusted girls who were devoted to their brother. They gave him the best room in their home, the six other members of the family crowding together in two rooms. The family had moved to the city from a rural area in order to provide better diabetic care for the boy.

Despite all this affection and attention, the patient remained an aloof, undemonstrative child. Neither physicians nor social workers were able to establish a close relationship with him. He left vocational high school in order to earn $8 a week as a butcher's helper. A set of polished butcher knives hung in a case on the wall of his room. Several times he was known to have expressed homicidal threats, not directed against any particular person. The definite schizoid pattern became more apparent as he passed through adolescence and at 18 years of age he was referred to a psychiatric institution. His intelligence quotient at age 17 was 89.

An attempt to escape regimentation resulted in wanderlust and in alcoholism in several patients.

M. P. (case 31), en route from Chicago to New York, suffered a severe reaction to insulin in Ohio. After recovery in a small hospital there, he found the surroundings so pleasant and the grass so green that he remained at the hospital until his funds were exhausted. He stated that it was the first time that he had ever known such luxury.

H. I. (case 16), (whose early history was cited on page 714, decided after graduation from high school to return home, but stayed only a short time, quarreling constantly with his mother and sisters. He then lived in rooming houses, making a living by selling magazine subscriptions. He traveled through the South by bus and truck. He held many positions for short periods and finally returned to New York complaining of failing vision. He reentered the hospital, where it was found

that he had extensive retinitis. He threatened to commit suicide and nearly succeeded by omitting insulin for a week. However, he recovered from diabetic coma and with the aid of excellent social service was rehabilitated. He lived in a dormitory for the blind, made a remarkable adjustment and became self supporting, selling stockings to nurses and to hospital employees. He recently married a nurse much against the wishes of both families. The only witnesses at the ceremony were his physician and a social worker.

S. E. (case 6), an adolescent, who learned to play several musical instruments, joined a jazz band and, at the age of 14, began to drink excessively.

E. L. (case 26), whose earlier years were described on page 713 sought release from the sordid life to which he was exposed. Alcoholism was first noted at 12 years of age and lasted until his environment was improved, that is, until his placement in a foster home.

In spite of some serious symptoms, we wish to stress the transient nature of most of the psychopathic phenomena observed during adolescence. In general these were exhibited by the patients who also had problems relating to their home environment. The combination of the physical complications of diabetes mellitus, unsatisfactory social adjustment and a general feeling of inferiority was responsible for the transient psychopathic states. The following case is illustrative.

R. K. (case 20) contracted diabetes at the age of 11 years. The family consisted of her parents, a brother, a sister and a maternal uncle who boarded with them. The father was a waiter, who earned only a modest living. He was particularly sensitive about being dependent on his wife's brother for financial help. The nature of the father's work kept him away from home every night so that his influence on the rest of the family was minimal. This was accentuated even further by his passive temperament which was overwhelmed by his wife's dominance. The mother was a highly neurotic but fairly intelligent woman who struggled to maintain a neat and clean home despite a multiplicity of psychogenic complaints. These gave her reasons to attend numerous clinics. She was an oversolicitous, overprotective parent but she displayed undisguised favoritism toward the younger and normal daughter. This daughter, 5 years younger than the patient, was unusually "spoiled" by the mother, who openly proclaimed her "the least troublesome of the children." She was indulged to such an extent that even such privileges as staying up late, denied the patient, were granted the younger nondiabetic sister. The patient expressed deep resentment and jealousy toward his sister but was extremely fond of the younger brother. The boy, eight years younger than the patient, was a puny, sickly child who became asthmatic. With the appearance of this chronic ailment, he too had severe behavior disorders and, like the patient, attended the Behavior Clinic, at Mount Sinai Hospital for some time. The patient "mothered" the boy, dressing and feeding him. She constantly accused her mother of neglecting him. In family quarrels the patient and her brother on the one side always opposed the mother and the sister on the other.

The development of diabetes apparently did not disturb the patient much, but the mother, in her solicitude, was overwhelmed by the care and attention required by the child. The mother constantly expressed anxiety and doubt as to her accuracy in weighing food. The tension of the home mounted progressively until at the end of the first year the mother wrote that she feared a "nervous break-

down." She described her daughter as given to frequent outbursts of temper and impudence, with constant threats of suicide. The two complained about each other continually when attending the clinic.

The patient entered high school at 13 years of age, expressing hopes of becoming a chemist. She was known as a "bookworm" and displayed a passionate interest in books on health. Her school work was satisfactory, but no close contacts were established with her classmates. Because of many symptoms of inadequate adjustment she was again referred to the Behavior Clinic. Soon after this she spent her first vacation at a summer camp for diabetic children and returned home "brighter and friendlier." The following year was noteworthy in that she developed close friendships with several other diabetic children attending the clinic, and, more important, formed attachments to her classmates. Her school work suffered, however, because of many absences due to recurrent infections of the upper respiratory tract. Her intelligence quotient at 16 was 114. She then expressed the desire to become a dietitian or a laboratory technician and seemed fascinated by hospital work. Her preoccupation with disease was indicated by the remarkably complete scrapbook which she maintained on matters pertaining to health and medical discoveries. As she developed an ever widening circle of friends of both sexes, her home life seemed happier. Her maturity was accompanied with increasing responsibility at home, with shopping, cleaning and generally helping her mother, who seemed more relaxed as the burden of diabetic care shifted to the patient. A more liberal prescription of the diet and the discarding of the practice of weighing the food further relieved both patient and mother. The mother began to respect her daughter's judgment and individuality.

A series of vocational interest tests was performed when the patient was 16½ years old. The total score showed a lack of ambition. She expressed keen interest only in nursing and bacteriology. The tests emphasized the narrow interests of the patient.

She completed the high school course but could not afford a college education, and her grades were not high enough to provide a scholarship. She felt unequal to the amount of study required in dietetic school or for laboratory training and realized that her ambitions were frustrated. At first she studied typewriting and shorthand in order to qualify for a clerical position, but soon economic pressure at home forced her to accept light manual factory work at $12 a week. She was so unhappy in this, her first position, that she lost weight, became asthenic and was sent to a convalescent home. On her return she applied for a civil service position and in 1942 became the first applicant with diabetes to be accepted by the Civil Service Commission of the United States. She was placed in the Brooklyn Navy Yard offices, where she seemed quite happy for almost a year. At that time she was offered a position at a higher salary with a business firm, where she has remained.

She had met a young German refugee, who seemed fond of her. They saw each other regularly until he was inducted into the army, and even then their meetings were still fairly frequent. During this period there had been no mention of diabetes or of marriage. R. K. was happy at work and gained weight, and her diabetes seemed less troublesome. She maintained a daily correspondence with her friend while he was overseas. She visited his parents weekly and enjoyed their company. After several months she began to display anxiety over the concealment of the diabetes. She had refrained from mentioning it to the young soldier before he had gone overseas because she felt that its presentation "would be easier in writing." After considerable delay and self reproach she

informed him that she had diabetes. He replied that the condition "made no difference" in his feelings toward her. Although this answer pleased her she felt guilty over the concealment. She expressed doubts as to the possibility of marriage, and she considered interruption of their correspondence. As her unhappiness increased, her depression deepened; she lost weight, slept poorly and was subject to "crying spells." She presented a picture of complete discouragement. Psychiatric assistance helped overcome her feeling of insecurity, and the depression vanished as prospects of her fiancé's early return seemed promising. At the present time she is happy at work, eagerly anticipating her forthcoming marriage.

INTELLIGENCE TESTS

Because the literature [9] contains conflicting statements concerning the intelligence of diabetic children, we attempted to obtain such data from our group.

Revised Stanford-Binet-Simon intelligence tests and vocational tests were given to 24 patients. The results of the tests are presented in table 2. Of the 24 patients, 20 had an intelligence quotient of 90 or

TABLE 2.—*Range of Intelligence Quotients of Twenty-Four Clinic Patients*

Intelligence Quotients	Patients	Total
70 - 80	2	4
80 - 90	2	
90 - 100	6	8 average
100 - 110	2	
110 - 120	4	12
120 - 130	4	
130 - 140	4	
	24	

more. Only 4 quotients fell below this figure. The mental level of the diabetic children and adolescents was similar to that of nondiabetic patients of the same ages who have been tested at our hospital.[10] These results demonstrated that young diabetic patients were neither "brighter" nor "duller" than normal.

None of the reported studies of the intelligence of diabetic children included reexaminations made after an interval of time. We investigated this aspect by repeating the Stanford-Binet test with 10 patients after an interval of several years. The intelligence quotients of 8 of them showed no significant alteration. There was a rise in one and a fall in another.

9. (*a*) Brown, G. D., and Thompson, W. H.: The Diabetic Child, Am. J. Dis. Child. **59**:238 (Feb.) 1940. (*b*) Grishaw, W. H.; West, H. F., and Smith, B.: Juvenile Diabetes Mellitus, Arch. Int. Med. **64**:787 (Oct.) 1939. (*c*) McGavin and others.[2] (*d*) Joslin and others,[7] p. 679.

10. Davis, R.: Personal communication to the authors.

ADJUSTMENTS

1. *Method of Evaluation.*—We have attempted to correlate a number of facts and have used the term "adjustment" to summarize our impressions of the reaction of the child to his diabetes, to his family and to society. Each child's adjustment was graded "excellent," "good," "fair" or "poor." This judgment was based on our personal impressions over many years of observation. Temperament and achievement were also considered in this evaluation. We considered "excellent" such patients as were happy at home, at school and at work, whose diabetes did not interfere with their daily life and who were able to live normally. The others were graded in relation to this superior group. Our tabulations were based on the status of the patients on Dec. 1, 1945. In general the patients with higher intelligence quotients made more satisfactory adjustments.

2. *Economic Status.*—Table 3 shows that the adjustment of private patients was "excellent" or "good" in contrast to that of the clinic or poorer group, in which fewer were well adjusted. We attempted to reclassify periodically the adjustments which our patients made.

TABLE 3.—*Adjustment of Clinic Versus Private Patients*

Adjustment	Clinic	Private	Total
Excellent	4	2	6
Good	9	4	13
Fair	11	2	13
Poor	10	1	11
Total	34	9	43

However, we found that the individual variations did not lend themselves to statistical evaluation. Some of the factors, such as maturity and marriage, usually improved the psychologic attitude, and, in contrast, blindness or other chronic complications naturally made it worse.

3. *Home Environment.*—Home environment included the economic status, harmony or lack of it among the members of the family and their reaction to the patient. When the home environment was excellent or good as it was in 23 instances (table 4), there were no poorly adjusted children, 16 being considered to show excellent or good and 7 fair adjustment. On the other hand, only 3 of the 20 from fair or poor homes could be considered well adjusted, the rest manifesting fair or poor adjustment. Socioeconomic factors were significant in influencing the behavior of juvenile diabetic patients, and were more important than for nondiabetic patients.

4. *Scholastic Achievement.*—It was noted that there were 18 diabetic patients whose scholastic achievement was good; 12 of these were doing fairly well, and 6 showed what was considered excellent achieve-

ment (table 5). Of these 18, 15 came from the well adjusted group as might be expected. On the other hand, of the 25 children with poor scholastic records, only 4 came from the well adjusted group; 11 came from the group with fair adjustment and 10 from the badly adjusted group. It is apparent therefore that scholastic achievement paralleled adjustment of the child and that both were directly related to the type of home and the economic status. Most of the children were able to attend school regularly and completed their studies satisfactorily.

TABLE 4.—*Adjustment of Patients Related to Home Environment*

Adjustment	Home Environment			
	Excellent	Good	Fair	Poor
Excellent	4	2	..	..
Good	3	7	1	2
Fair	..	7	3	3
Poor	..	..	3	8
Total	7	16	7	13

There were some who fell behind because of frequent illness, often the result of a diabetic complication. On the other hand, others who had no interest or capacity for school welcomed any opportunity to avoid it. For example, although the main diabetic clinic session at the hospital was held on Saturday mornings so as not to interfere with school attendance, these patients deliberately chose to come to the clinic on week days.

TABLE 5.—*Adjustment of Patients Related to Scholastic Achievement*

Adjustment	Scholastic Achievement			
	Excellent	Good	Fair	Poor
Excellent	5	1	..	..
Good	1	8	4	..
Fair	..	2	5	6
Poor	..	1	3	7
Total	6	12	12	13

5. *Manual Achievement.*—In general, tests for manual dexterity gave results similar to those obtained with the Binet-Simon test. There were, however, some exceptional instances in which poor mental capacity was accompanied with remarkable manual dexterity.

M. B. (case 4), who by the Stanford-Binet test had an intelligence quotient of 72 at the age of 16 (mental age of 10), displayed unusual manual ability in mechanical assembly and paper folding. M. P. (case 31) had no intellectual ambition whatsoever but willingly accepted unremunerative heavy manual work.

These cases illustrate a fact well known to vocational guidance advisers, namely, that patients with dull mentality do not find monotonous work

irksome. The development of special skills was encouraged in such children by sending them to vocational high schools.

6. *Occupations.*—Forty-two per cent of the patients reported on by Eisele [11] from the clinic of the New England Deaconess Hospital were college graduates. Our patients were younger; many were still attending high school. Only 4 of our patients have completed college. The others because of their economic status were forced to enter industry in order to support their families, after completing high school.

None of the 43 patients has achieved anything approaching outstanding success. However, the group is still young and is handicapped economically and socially. During adolescence there was a striking tendency to seek employment in food industries. Most of them were employed as soda fountain clerks, sandwich makers, ice cream and orangeade venders, candy salesmen and butchers' helpers. Some of the girls expressed the desire to become nurses or dietitians, yet none actually did so. As the patients became older and acquired skills, most of the girls became clerks and saleswomen and the boys chose light mechanical or clerical work. A tendency to change positions frequently, a characteristic of youth, was noted. Some patients avoided applying for positions which required physical examinations and, if eager for a certain job, resorted to subterfuge for the urinalysis. Many of the patients felt that public knowledge of their being diabetic might jeopardize their business opportunities. However, even after employment had been obtained, our patients were fearful that their illness become known.

Examples of concealment included: the secretary of a newspaper executive, M. J. (case 17); a business machine operator in a Wall Street firm, M. T. (case 42); a salesgirl in a department store, G. K. (case 19), and a shipping clerk in a clothing firm, H. C. (case 5).

S. S. (case 36), another salesgirl, became panicky when she recognized the physician who was treating her as he entered the store in which she was employed. Glancing fearfully at the other employees, she whispered the followng greeting, "Please forgive me for not calling you 'Doctor' here; I don't want the others to know I'm sick."

It is commendable to note that the Federal government permits applicants with diabetes to qualify for civil service positions. G. S. (case 37) and R. K. (case 20) held such positions. Further extension of this progressive step would be of great value to the large numbers of diabetic persons seeking employment today.

MARRIAGES AND BIRTHS

The fears and anxieties regarding marriage which were expressed during adolescence were accentuated as adulthood approached. Nine

11. Eisele, H. E.: The Juvenile Diabetic Patient Surviving Twenty Years, J. A. M. A. **120**:188 (Sept. 19) 1942.

male and 5 female patients of our series married (table 6). The attainment of marriage seemed more difficult for the girls. As 1 of our patients, S. S. (case 36), expressed it, "a girl with diabetes has two strikes against her when it comes to getting marrried." This girl was engaged to be married on three occasions, yet each suitor revoked his proposal on learning of her diabetes. Her growing cynicism was expressed by her statement, "I will not tell the next one until I have the wedding ring on my finger." This unmarried girl unfortunately became pregnant and died after a therapeutic abortion. Although the girls desired marriage, more so than the boys, many of them felt or

TABLE 6.—*Marriages and Births*

Patient	Case	Adjustment	Year of Marriage	Births	Success of Marriage	Type of Work of Mate	Personality of Mate
Female patients							
S. G.	10	Fair	1937	1 mis. 1 still.	Good	Mechanic	Understanding
E. H.	11	Fair	1936	None	Good	Electrician	Average
M. K.	18	Excellent	1934	1 mis. 1 still.	Good	Optical lens worker	Intelligent
E. S.	38	Good	1941	None	Separated	Civil service	Intelligent
J. Z.	43	Poor	1939	1 child 1 mis.	Poor	Salesman	Unintelligent, unsympathetic
Male patients							
H. C.	5	Good	1943	None	Good	Housewife	Very young, immature
N. G.	7	Fair	1944	None	Poor (separated)	Housewife	Intelligent, solicitous
G. H.	14	Good	1940	None	Good	Secretarial	Superior, understanding
A. N.	30	Good	1942	1 child	Good	Housewife	Understanding, helpful
G. S.	37	Excellent	1945	None	Not certain (too recent)	Housewife	Sympathetic
M. T.	42	Good	1943	1 child	Good	Housewife	Intelligent
J. M.	29	Excellent	1945	None	Not certain (too recent)	Housewife	Fairly intelligent
H. I.	16	Good	1945	None	Not certain (too recent)	Nurse	Sympathetic, intelligent
E. L.	26	Fair	1944	1 child	Poor (separated)	Unknown	Unknown

expressed a distinct apprehension about it. Their fears were concerned with the burdens of diet and insulin as well as the possibility of transmitting diabetes to their offspring. This fear was an extremely difficult one to overcome. Patients faced an additional problem because of a lack of intelligent understanding, sympathy and cooperation on the part of parents-in-law, who frequently resented the fact that their nondiabetic child had assumed a lifelong burden. Thirteen of the diabetic patients married into families that were not diabetic as far as is known. The fourteenth patient was able to marry only because his fiancée understood and accepted his problem, her own father being diabetic. However,

despite drawbacks, we have been gratified that most of the marriages thus far seem to have been reasonably happy ones. All but 2 of the married patients were in the well adjusted or moderately well adjusted group before marriage. Two male patients, N. G. (case 7) and E. L. (case 26), and 1 female (E. L. case 38) became separated within two years after marriage.

With respect to child bearing, the experience of this group has not been gratifying. Only one living child was born to 3 female patients, each of whom became pregnant twice. Thus, of the six pregnancies, five terminated in stillbirths and miscarriages. Two other female patients have not as yet become pregnant. The 2 patients who failed to bear living children were greatly depressed by their misfortune. Fortunately, both were able to adopt infants through the aid of social agencies.

Of the 9 male patients 3 became fathers; the wives of 5 have not become pregnant as yet, and 1 patient has been reluctant to assume the responsibility of parenthood because he has both diabetes and tuberculosis.

The disappointing record of childbirths of this group can be explained by a number of factors. The long duration of diabetes (average fifteen years) and the onset of degenerativve changes are important general causes of the high fetal and neonatal mortality. Because of the lack of an obstetric department in our hospital the patients were transferred to other hospitals with interruption of continuity of the diabetic regimen.

COMMENT

Previous publications in our opinion have inadequately presented the influence of the disease on the behavior of young diabetic patients. Joslin,[12] for example, devoted a single paragraph to the psychologic problems of the diabetic child and a few sentences to their mental adjustments. Duncan [13] likewise discussed the subject briefly. Others [14] did not mention it at all or limited their studies to a few years.[15] Loughlin and Mosenthal [8] made a report on the personalities of diabetic children at a summer camp (Camp Nyda, at Burlingham, N. Y.) during a brief vacation.

It is obvious that short term observations such as these give only a partial view of an ever changing panorama. Trite expressions such as "diabetic children are unusually bright" are incorrect when one

12. Joslin and others,[7] p. 690.

13. Duncan, G. G.: Diseases of Metabolism, Philadelphia, W. B. Saunders Company, 1942.

14. (*a*) Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1941. (*b*) Wirtschafter, Z. T., and Korenberg, M.: Diabetes Mellitus, Baltimore, Williams & Wilkins Company, 1942.

15. McGavin and others.[2] Brown and Thompson.[9a] Grishaw and others.[9b]

studies these patients carefully over long periods. One of the children observed briefly by Loughlin and Mosenthal was classified as a "normal, ideal boy," but within two years he exhibited a psychopathic personality for which he was treated at Bellevue Hospital.

The present report and also those of Eisele [11] and Rosenbusch [16] differ from those just mentioned in that the psychologic and personality reactions of diabetic children have been carefully followed through years of childhood, adolescence and early adult life. Rosenbusch's studies are most thorough. He followed a group of 88 children for as long as twenty years.

With the exception of Brown and Thompson [9a] the authors cited concurred in the opinion that personality changes and maladjustments were to be expected in the life of the diabetic child. Brown and Thompson found "no characteristic abnormalities in personalities." Their analysis was based on the initial examination and follow-up reports from schools and parents. It seems likely that subsequent personal examinations of their patients eventually would have revealed abnormalities not present at the earlier examination. Rosenbusch [16] found "psychopathological behavior in a number of patients."

McGavin and coworkers [2] stated that children who had intelligence tests were neither significantly brighter nor duller than nondiabetic children. Brown and Thompson found that their patients were distributed normally with regard to intelligence. Brown and Thompson further explained Joslin's [9d] report of higher intelligence quotients among his patients on the basis of a selection from an upper socioeconomic group. Rosenbusch [16] also found average intelligence among his patients. Grishaw and others [9b] found a higher intelligence quotient than normal in 62 "unselected" patients. We could find no significant difference in the intelligence as determined by the Stanford-Binet test in 24 diabetic patients attending the outpatient clinic as compared with a similar group of nondiabetic patients tested by the same psychologist.

This survey would be incomplete were we not to call attention to the fact that diabetes is similar to other chronic illnesses in its effect on the psyche. Just as a hunchback or a cripple is always aware of his deformity, so the diabetic child is always conscious of his condition. He cannot escape the daily injection and is constantly reminded of his affliction by the discomfort produced by the needle as well as by the restriction in diet. Furthermore, in many persons each dose injected is associated with the fear of a possible hypoglycemic reaction. When behavior disorders arise in homes where there is conflict and insecurity, the reaction is the more serious. Conversely, an ideal adjustment is possible if there is understanding, harmony and security in the home.

16. Rosenbusch, H.: Prognose und Spätkomplikationen des Diabetes Mellitus im Kindesalter, Ann. pædiat. **164**:225 and 281, 1945; **165**:12, 1945.

SUMMARY

.The problems which arose in 43 young diabetic patients from childhood through adolescence to maturity have been analyzed. No patient who had not been observed for at least ten years was included in this report.

The type of home, its economic security and the contacts at school and in social life, all had especial influence on the reaction of the diabetic child to his disease.

Specific problems of childhood became less disturbing with the onset of maturity. During adolescence, problems relating to vocation and marriage appeared. Maturity usually brought about improvement in behavior, with the desire for independence being its outstanding characteristic. Marriage for the young diabetic person was difficult, especially for the young women. However, most of the marriages have been happy ones.

The specific effects of diabetes on behavior were found to be unrelated to the age of onset, the duration or the severity of the disease.

Diabetic regimentation, while necessary at first, produced behavior difficulties.

The immediate and the more remote or cumulative effects of hypoglycemia on the brain were considered to be potentially serious.

Psychopathic behavior in a serious form was exhibited in 3 patients; other minor behavior disturbances were frequent.

The results of intelligence tests were not significantly different from those of tests given to a similar socioeconomic nondiabetic group. No demonstrable change was noted in those patients who were retested. The patients in the better economic group and with better home environment had higher intelligence quotients and made more satisfactory adjustments to diabetes.

CONCLUSION

Diabetes mellitus produces many psychologic problems which may result in abnormal behavior throughout childhood, adolescence and adult life.

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Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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AND
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BALTIMORE

(Continued from Page 625)

PENICILLIN THERAPY

Only in England, where penicillin was discovered, and in the United States, where its usefulness in syphilis first was demonstrated, has penicillin been used extensively in the treatment of syphilis. In other countries, either penicillin has been unavailable or its use has been restricted to more acutely lethal infections. Consequently, information concerning the treatment of syphilis with penicillin thus far has appeared only in British and American journals. Summaries of recent developments without original observation have recently appeared in the Latin-American,[93] French [94] and Indian [95] literature.

In the United States, a nationwide study of the effect of penicillin in the treatment of syphilis was begun Sept. 1, 1943, under the auspices of the Committee on Medical Research. On Jan. 1, 1946, the financing and general supervision of the project were taken over by the National Institute of Health, United States Public Health Service. Prior to this date the study was directed by the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council, and subsequently by the Syphilis Study Section of the National Institute of Health. Participating in the study are forty-one clinics and seven laboratories of experimental syphilis. As a result of their collective and cooperative efforts, an enormous amount of factual data has been compiled. Few if any new therapeutic agents have been studied so extensively in such a brief period as has penicillin in its relation to syphilotherapy.

93. Castanedo y Pardo, C.: Penicillina y sífilis, Rev. sif., leprol. y dermat. **2**: 101 (June) 1945. Pardo Castello, V.; Ferrer, I., and Castenedo, C.: La penicillina en tratamiento de la sífilis, Rev. sif., leprol. y dermat. **3**:5 (Jan.) 1946.

94. Marshall, J.: Le traitement de la syphilis par la pénicilline, Ann. de dermat. et syph. **9-10**:228 (Sept.-Oct.) 1945. de Gennes, L., and Cournot, L.: Le traitement de la syphilis par la pénicilline, Presse méd. **24**:344 (May 25) 1946.

95. Nair, V. G.: Penicillin in the Treatment of Venereal Diseases, Indian J. Ven. Dis. **11**:69 (Oct.-Dec.) 1945.

The Chemistry of Penicillin and the Pharmacology of the Several Penicillin Fractions.

During World War II, many laboratories in the United States and Great Britain participated in an extensive study of the chemistry of penicillin. Censorship of the project was carefully maintained, and the secrecy has proved to have been a double-edged sword. It had the somewhat dubious virtue of withholding information that might conceivably have given "aid and comfort to the enemy." It also had the disadvantage of delaying scientific progress by withholding important knowledge from competent investigators.

Be that as it may, some time after the cessation of hostilities medical knowledge formerly considered "secret" was gradually released. There recently appeared a statement issued jointly by the American Committee on Medical Research [96] and the British Medical Research Council [97] concerning the chemistry of penicillin.

The details of this summary are more relevant to the work of the research chemist than to the medical practitioner. It is of interest, however, that penicillin is thought to have the empiric formula $C_9H_{11}O_4SN_2R$, the differences between various penicillin species depending on a substituent group in the molecule. (In penicillin G, this substituent represents a benzyl group; in penicillin F, *n*-amyl; in penicillin X, p-hydroxy-benzyl, and in penicillin K, *n*-heptyl.) Each species can be converted into various metallic salts or esters. The precise structural formula of penicillin is still undetermined, however, and its synthesis has not yet been formally announced.

As information regarding the various penicillin species increased and as data relative to the chemistry of penicillin gradually became available, there was accumulating evidence that changes were occurring in the character of the commercial product. Physicians who had been using penicillin for various infections became aware of the increasing doses required to accomplish the therapeutic results they had become accustomed to expect. This decline in the effectiveness of commercial penicillin soon was manifested by increasingly high relapse rates in early syphilis, and it was in the cooperative study of this condition that the changing character of penicillin first was suggested and quantitated.

The details of the fascinating story, which reads like detective fiction, of how this information was uncovered and of how the evidence was logically analyzed step by step, have been published in a joint state-

96. Chemistry of Penicillin, Committee on Medical Research, Washington, and Medical Research Council, London, Science **102**:627 (Dec. 21) 1945.

97. Chemistry of Penicillin, Medical Research Council, London, and Committee on Medical Research, Washington, Nature, London **156**:766 (Dec. 29) 1945.

ment [98] by the Committee on Medical Research, the United States Public Health Service and the Food and Drug Administration.

It was shown that the results of penicillin therapy in early syphilis have been distinctly less favorable since May 1944 than prior to that date, almost surely because there have occurred, as a result of certain changes in the manufacturing processes designed to increase the yield and the "purity" of the product, alterations in the character of commercial penicillin. These changes were in two directions: (1) a change in relative quantities of penicillin species, with a probable substantial decrease in the amount of penicillin G and an equal compensatory increase in the amounts of penicillins F and K, especially the latter, and (2) the increasing purity of penicillin in terms of units per milligram and a corresponding decrease of impurities that possibly have therapeutic activity. All the recent information indicates that the first of these two changes is by far the more important.

It has been suggested [99] that crystalline forms of penicillin may be less effective against syphilis than partially purified preparations. As reported by Williamson and Lourie,[100] however, so far as therapeutic trials against Borrelia recurrentis infections in mice may be an index of the true situation, there is no superiority of partially purified preparations over crystalline penicillin G. Penicillin X was found less efficacious than penicillin G in the treatment of these spirochetal infections in mice.

The results of studies in which the various penicillin fractions are compared in respect to their activity in vitro or in vivo must be interpreted with due regard to whether the comparison is on an Oxford unit for unit basis or in gravimetric terms, involving comparable weights.

Libby and Holmberg,[101] for example, have found evidence that, milligram for milligram, penicillin G is more efficacious in vitro against Staphylococcus aureus and Bacillus subtilis and that the X fraction is superior against pneumococci, streptococci and Escherichia coli.

98. The Changing Character of Commercial Penicillin, with Suggestions as to the Use of Penicillin in Syphilis, Committee on Medical Research, the United States Public Health Service and the Food and Drug Administration, J. A. M. A. **131**:271 (May 25) 1946.

99. Dunham, W. B., and Rake, G.: The Relative Activity of Partially Purified Penicillin and of Crystalline Penicillin G on Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **29**:214 (March) 1945.

100. Williamson, J., and Lourie, E. M.: Therapeutic Action of Different Penicillins on Spirochaeta Recurrentis Infections in Mice, Brit. M. J. **1**:828 (June 1) 1946.

101. Libby, R. L., and Holmberg, N. L.: The Activity of Penicillins G and X in Vitro, Science **102**:303 (Sept. 21) 1945.

Ory, Meads and Finland [102] report that, when tested with preparations containing 65 per cent or more of penicillin X and with commercial lots which were almost entirely pencillin G, hemolytic streptococci, gonococci and meningococci were (in terms of Oxford units) from two to eight times more sensitive to penicillin X, pneumococci and Streptococcus viridans were twice as sensitive to penicillin X and most staphylococci were equally sensitive to the two kinds of penicillin. Levels of penicillin activity in the serum were higher and sustained longer after intramuscular injections of pencillin X than after injections of the same number of units of "regular" penicillin.

A preliminary clinical trial indicated to the authors that:

Penicillin X is nontoxic and at least as effective as regular penicillin in the same doses in cases of pneumonia and probably more effective in gonococcic infections. Further trials with the use of smaller doses and longer intervals are necessary in order to establish the therapeutic superiority of penicillin X.

In an in vivo study, Richardson and his associates [103] have compared the spirocheticidal activity against Clostridium oedematiens of four preparations of penicillin varying in degree of purity and containing varying proportions of penicillin G and other penicillins. On the basis of dosage in Oxford units, no differences were noted among the four samples, regardless of the method of administration.

In the treatment of experimental syphilis, penicillin K has been far less efficient [104] than other penicillin compounds. This low therapeutic activity of penicillin K has been found by Eagle and Musselman [105] to be due to the fact that penicillin K disappears from the blood more rapidly than do the other penicillins. One hour after the injection into rabbits or human beings of penicillins G, F, X and K, blood levels of penicillin K were one fourth to one eleventh of those observed with the other penicillins, and pencillin K persisted at demonstrable levels for relatively short periods. The recovery of penicillin K in the urine averaged only 30 to 35 per cent, whereas the average recovery of penicillins G, F and X was 74 per cent in rabbits and 91 per cent in human beings.

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102. Ory, E. M.; Meads, M., and Finland, M.: Penicillin X: Comparison with Penicillin G with Respect to Sensitivity of Pathogenic Organisms and Serum Levels, J. A. M. A. **129**:257 (Sept. 22) 1945.

103. Richardson, A., P.; Walker, H. A.; Loeb, P., and Miller, I.: The Experimental Basis for the Quantitative Chemotherapy of B. Novyi in Mice with a Comparison of Action of Penicillin and Dichlorphenarsine Hydrochloride, J. Pharmacol. & Exper. Therap. **85**:23 (Sept.) 1945.

104. Chesney, A. M.: Unpublished data. Mahoney, J. F., and Arnold, R. C.: Unpublished data.

105. Eagle, H., and Musselman, A.: The Low Therapeutic Activity of Penicillin K Relative to That of Penicillins, F, G, and X, and Its Pharmacological Basis, Science **103**:618 (May 17) 1946.

Coghill, Osterberg and Hazel[106] have confirmed this important observation. In their study, the preparations used were analytically pure crystalline penicillins G, X and K. Twenty-five thousand units were injected intravenously and concentrations of penicillin in the blood and urine determined at suitable intervals. The duration of penicillin blood levels of at least 0.03 unit per milliliter for each of the penicillins was G, two to two and one-half hours; X, four to four and one-half hours, and K, one-half to three-fourths hour. The inefficient action of penicillin K as compared with the action of penicillins G and X is explained by comparison of the urinary excretions. During the first two hours, 83 per cent of penicillin G was excreted, 78 per cent of penicillin X and only 28 per cent of penicillin K.

These data indicate that penicillins G, F and X are of sufficient stability in the human body that the maintenance of adequate blood levels is conditioned almost entirely by the amount lost by excretion in the urine and that penicillin K is inactivated in the body more rapidly and to a greater extent than penicillins G, F and X. Of considerable practical importance is the fact that, because of its low therapeutic value, the amount of penicillin K in commercial penicillin should be kept minimal.

It should be stressed, in view of the publication in the lay press of a sensationalized and inaccurately presented article,[107] that the penicillin manufacturers are aware of the situation, are cooperating in the study of penicillin fractions and are taking practical steps to correct the identifiable difficulties in production.

Mode of Action.

The precise way in which penicillin acts to destroy T. pallidum is still unknown. Frazier and Frieden,[108] who have reviewed the published information pertaining to the mechanism of its action, state the belief that penicillin acts chiefly as a bactericidal, and therefore presumably spirocheticidal, agent. Data pointing to a spirochetistatic action of penicillin are not lacking, however, and the authors themselves report changes in the structure of spirochetes obtained from patients under treatment with penicillin. In 5 patients, it was observed that as treatment progressed there was a relative increase in the number of long forms of the spirochete. The increase was progressive within limits until organisms no longer could be found in dark field preparations. The long forms were, in general, less motile than short

106. Coghill, R. D.; Osterberg, A. E., and Hazel, G. R.: The Relative Effectiveness of Pure Penicillins G, X and K, Science **103**:709 (June 14) 1946.

107. Deutsch, A.: Plan National Roundup of Syphilis Victims Endangered by Treatment with Penicillin K, PM Daily **6**:13 (April 22) 1946.

108. Frazier, C. N., and Frieden, E. J.: Action of Penicillin, Especially on Treponema Pallidum, J. A. M. A. **130**:677 (March 16) 1946.

forms and occasionally were angulated at the middle. In the light of this finding, the writers speculate as to whether the elongation of spirochetes observed in these cases "may not be an indication of excessive growth and delayed cellular division."

While penicillin-resistant strains of bacteria such as the staphylococcus, pneumococcus, streptococcus and gonococcus can be produced in vitro, little is known about the adaptability of spirochetal organisms to this antibiotic agent. To elucidate this problem, Tsun and Frazier [109] have made in vitro studies on the adaptability of the Reiter strain of cultured spirochetes to increasing amounts of penicillin. In attempting to increase the resistance to penicillin of these spirochetes, the authors were faced with the difficulty of overcoming the slow rate of growth. This long period of growth resulted in some deterioration of the antibiotic agent at the temperature of incubation (37 C.). Even with these unfavorable factors, they were able to demonstrate that the Reiter strain of so-called T. pallidum did not develop an increased tolerance to penicillin after being subjected to fifteen consecutive passages through mediums containing penicillin. The effect of penicillin on the spirochetes appeared to involve an inhibition of cellular division, with resulting elongation and early death of the spirochetes observed in fresh cultures containing penicillin. Electron microscopic studies revealed that the long forms which developed after exposure to penicillin had lost their flagella.

Thus, although bacteria have been made resistant to penicillin in the test tube, there is yet no evidence that spirochetal organisms become penicillin fast. Thus far at least, penicillin resistance has not been a problem in syphilis. As more definitive information is lacking on the optimum time-dose relationships involved, it is, of course, difficult to define precisely what constitutes "penicillin resistance." The report of Tyson [110] is entirely unconvincing.

Tainter [111] summarized the problems of bacterial "fastness" to sulfonamide drugs and to penicillin. He states the belief that there is no indication that the mechanism involved in the development of penicillin resistance is the same as that in the case of resistance to the sulfonamide compounds, particularly if the importance of para-aminobenzoic acid is granted. Penicillin apparently blocks the growth of organisms by interfering with the process of division. It has only

109. Tsun, T., and Frazier, C. N.: Penicillin Sensitivity and Morphology of the Reiter Strain of Treponema Pallidum After Cultivation in Media Containing Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **30**:205 (May) 1946.

110. Tyson, W. G.: Early Syphilis Resistant to Treatment with Penicillin, J. Invest. Dermat. **6**:279 (Oct.) 1945.

111. Tainter, M. L.: A Summary of the Problems of Sulfa and Penicillin Fastness, New York State J. Med. **45**:2509 (Dec. 1) 1945.

weak action on spores and little effect on organisms in the resting phase. In some respects, penicillin behaves as an enzyme rather than as a compound which is used up in producing its physiologic effect. The question of how micro-organisms become resistant to the action of penicillin has as yet not been satisfactorily answered. The author critically analyzes the proposed explanations for the phenomenon. The prevention of the development of penicillin-fast strains of micro-organisms is important if penicillin is to continue as highly successful as it is at present. It is suggested that the use of effective doses from the onset of treatment is desirable. Ineffectual dosages, especially those which result from self medication, are deplored.

Dosage.

Raiziss'[112] experiments with a limited number of animals indicate that in rabbits syphilitic infections apparently are cured by 40,000 Oxford units of penicillin per kilogram of body weight given over a period of eight days, whether in aqueous solution or in oil suspension. Translated into a treatment schedule for human beings of 60 Kg., the total dose for the patient would be 2,400,000 units. Since, however, larger doses of penicillin appeared to cause more rapid healing of lesions and probably to compensate for differences between human and rabbit syphilis, the author recommends that the "total treatment" for a patient weighing 60 Kg. be 4,800,000 units of penicillin.

Methods of Administration.

Turton[113] has found that continuous intramuscular infusion is a practicable method of administering penicillin in a busy hospital ward. Hirsh and Dowling[114] also conclude that continuous intramuscular infusion is the method of choice for the parenteral administration of penicillin. These authors employed continuous intramuscular administration of penicillin in 110 patients, without deleterious effects except for mild to moderate pain in 6 patients. Pain usually could be prevented by changing the site of injection occasionally and by the addition of procaine hydrochloride to the infusion.

In maintaining consistently high serum levels of penicillin, Loewe and his associates[115] found the continuous intravenous drip superior

112. Raiziss, G. W.: The Effect of Penicillin in Experimental Rabbit Syphilis, Science **102**:329 (Sept. 28) 1945.

113. Turton, E. C.: Administration of Penicillin by Intramuscular Infusion, Brit. M. J. **2**:283 (Sept. 1) 1945.

114. Hirsh, H. L., and Dowling, H. F.: Observations on the Continuous Intramuscular Method of Administering Penicillin, Am. J. M. Sc. **210**:435 (Oct.) 1945.

115. Loewe, L.; Rosenblatt, P.; Russell, M., and Alture-Werber, E.: The Superiority of the Continuous Intravenous Drip for the Maintenance of Effectual

(Footnote continued on next page)

to fractional intramuscular or continuous intramuscular methods of injection.

Ory and his co-workers [116] also determined penicillin levels in blood serum following administration by a variety of routes. In contradistinction to the aforementioned reports, these workers found that serum levels following continuous intravenous or continuous intramuscular administration usually were no higher than those following intermittent intramuscular injection of comparable doses at two hour intervals, provided the fluid intake was restricted. With both continuous intravenous and continuous intramuscular infusions, serum levels were fairly constant in one person but variable among different patients on the same dosage.

On the hypothesis that continuous levels of penicillin in the blood stream may not be necessary in the treatment of syphilis and hoping to evolve a time-dose relationship for administering sodium penicillin suitable for ambulatory patients, two groups of English workers have utilized schemes of intermittent penicillin therapy.

Lourie and his associates [117] treated 17 patients with early syphilis by the administration of three doses of 600,000 units of sodium penicillin at hourly intervals, given on five successive days. In each case, infectious lesions disappeared and seronegativity was attained.

Lloyd-Jones, Allen and Donaldson [118] treated 215 patients with early syphilis by single daily injections of sodium penicillin. Individual injections were of 300,000 or 500,000 units and the duration of therapy from five to fifteen days. In one series, penicillin was given intravenously; in another, the intramuscular route was utilized. The immediate response was similar to other forms of penicillin therapy: spirochetes disappeared, the lesions healed and serologic reactions became negative. When daily injections of 300,000 units were given intravenously, an infectious relapse rate of 9 per cent was observed. With the same amounts given intramuscularly, 5.5 per cent of the patients had early relapses. When the daily injections were each of 500,000 units, the relapse rate was lower. Thirty additional patients were treated with 3,000,000 to 5,000,000 units of penicillin administered as massive

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Serum Levels of Penicillin: Comparative Studies with Particular Reference to Fractional and Continuous Intramuscular Administration, J. Lab. & Clin. Med. **30**:730 (Sept.) 1945.

116. Ory, E. M.; Meads, M.; Brown, B.; Wilcox, C., and Finland, M.: Penicillin Levels in Serum and in Some Body Fluids During Systemic and Local Therapy, J. Lab. & Clin. Med. **30**:809 (Oct.) 1945.

117. Lourie, E. M.; Ross, A. O. F.; Nelson, R. B.; Collier, H. O. J., and Robinson, D. T.: Ambulatory Treatment of Early Syphilis with Penicillin, Lancet **2**:696 (Dec. 1) 1945.

118. Lloyd-Jones, T. R.; Allen, S. J., and Donaldson, E. M.: Out-Patient Treatment of Early Syphilis with Penicillin, Brit. M. J. **1**:567 (April 13) 1946.

single doses, repeated daily for from one to five days. With these time-foreshortened schedules, relapse rates were between 50 and 100 per cent.

Intrathecal Administration.—It has been demonstrated repeatedly that penicillin does not penetrate into the cerebrospinal fluid in appreciable amounts after intramuscular or intravenous injection. McDermott and Nelson,[119] using dilution technics of bioassay, were unable to demonstrate penicillin in spinal fluids obtained from 70 patients who had received intramuscular injections of doses as high as 500,000 Oxford units. At concentrations of 0.078 to 1.25 units of penicillin per cubic centimeter of blood serum, penicillin was found to diffuse through artificial membranes in vitro and into ascitic fluid in vivo. Thus the failure of penicillin to appear in the cerebrospinal fluid seemed not to be because it is bound significantly to nondiffusible elements in serum.

Kaplan and his associates [120] report that examination of spinal fluids of 12 neurosyphilitic patients from ten to one hundred and fifty minutes following intramuscular administration did not reveal the presence of penicillin (within the limits of the test employed, i. e., less than 0.125 unit per cubic centimeter).

Dumoff-Stanley and her co-workers [121] also conclude that the systemic administration of penicillin in the doses commonly employed does not consistently yield measurable concentrations of the drug in the cerebrospinal fluid.

With penicillin therapy in massive doses by continuous intravenous drip (10,000,000 to 25,000,000 units given over a period of twenty-four hours), Schwemlein and his associates [122] were able to demonstrate measurable concentrations in the cerebrospinal fluids of 126 of their 162 patients (77.7 per cent). There was a direct relationship between the total dosage and the observed levels of penicillin in the spinal fluid but no clear correlation between blood and cerebrospinal fluid levels.

Seeking to determine whether the presence of inflammation of the meninges is an important factor in the penetration of penicillin into the

119. McDermott, W., and Nelson, R. A.: The Transfer of Penicillin into the Cerebrospinal Fluid Following Parenteral Administration, Am. J. Syph., Gonor. & Ven. Dis. **29**:403 (July) 1945.

120. Kaplan, L. I.; Read, H. S.; Becker, F. T., and Seymour, C. F.: The Concentration of Penicillin in the Spinal Fluid Following Intramuscular Administration in Neurosyphilis: A Negative Report, J. Lab. & Clin. Med. **31**:317 (March) 1946.

121. Dumoff-Stanley, E.; Dowling, H. F., and Sweet, L. K.: The Absorption into and Distribution of Penicillin in the Cerebrospinal Fluid, J. Clin. Investigation **25**:87 (Jan.) 1946.

122. Schwemlein, G. X.; Barton, R. L.; Bauer, T. J.; Loewe, L.; Bundesen, H. N., and Craig, R. M.: Penicillin in Spinal Fluid After Intravenous Administration, J. A. M. A. **130**:340 (Feb. 9) 1946.

cerebrospinal fluid, Kinsman and D'Alonzo [123] performed spinal fluid assays on 2 patients with tuberculous meningitis, 9 with meningococcus meningitis and, as controls, approximately 20 patients with early syphilis without meningitis. In none of the patients used as controls could penicillin be detected in the cerebrospinal fluid. In the presence of meningitis, after large intramuscular doses, penicillin occasionally was found in the spinal fluid, but its appearance was irregular and never in excess of 0.05 units per cubic centimeter. The spinal fluids of 4 patients with meningococcic meningitis were examined after the intrathecal injection of 10,000 units. After eight hours, the spinal fluid contained 3.9 to 20.0 units per cubic centimeter and after twenty-four hours 0.078 to 0.312 unit per cubic centimeter. In the light of this finding, the authors suggest that intrathecal injections of penicillin need not be repeated oftener than once every twenty-four hours.

Since penicillin does not penetrate the subarachnoid spaces in appreciable quantities following extrathecal injection and since its excretion following intrathecal administration is delayed, there might appear to be certain theoretic advantages of the latter route of administration in the treatment of neurosyphilis.

There are, however, certain objections to the subarachnoid administration of penicillin. From the clinic and from the experimental laboratory [124] have come additional reports of convulsive seizures, signs of meningeal irritation and other untoward reactions following intrathecal use.

That the phenomena are not due to impurities in the preparations used has been shown by Walker and his colleagues,[125] who have encountered untoward reactions with penicillin made by ten different manufacturers and with purified crystalline penicillin.

Despite these reports of untoward reactions, the intrathecal administration of penicillin has been used by some investigators, and their early results have been reported favorably. Thrasher,[126] for instance, has made a preliminary report on 70 patients with various forms of neurosyphilis treated by the intrathecal administration of penicillin. The weekly intrathecal administration of penicillin in doses of 20,000 units apparently

123. Kinsman, J. M., and D'Alonzo, C. A.: The Penetration of Penicillin Through Normal and Inflamed Meninges, New England J. Med. **234**:459 (April 4) 1946.

124. Miller, L. S.: Intracisternal Penicillin: Observations of Its Effect on Dogs, J. Pediat. **28**:671 (June) 1946.

125. Walker, A. E.; Johnson, H. C.; Case, T. J., and Kollros, J. J.: Convulsive Effects of Antibiotic Agents on the Cerebral Cortex, Science **103**:116 (Jan. 25) 1946.

126. Thrasher, J. R.: Intrathecal Penicillin in Cerebral Spinal Syphilis, J. Indiana M. A. **38**:216 (July) 1946.

was well tolerated, although toxic reactions are not detailed. Weickhardt [127] expresses the opinion that intrathecal injections of therapeutically effective amounts of penicillin may be given provided that a series of gradually increasing small doses has been tolerated. Gradual elevation of dosage is regarded as a significant factor, small initial doses perhaps serving to "desensitize" neural tissues to the drug. Four paretic patients with no history of convulsions were treated with intrathecal administration of penicillin alone, and favorable results were obtained clinically and at examination of spinal fluid.

Nevertheless, the incidence of untoward reactions plus the necessity of frequently repeated lumbar punctures has discouraged the use of massive doses of penicillin by the intrathecal route. In view of the distinctly favorable results that have been observed after intramuscular or intravenous injection, subarachnoid administration seems undesirable except, perhaps, in certain exceptional cases in which the conditions fail to improve after therapy with parenterally administered penicillin.

Oral Administration.—It has long been known that the oral administration of penicillin is less satisfactory than is parenteral injection. Many attempts have been made to increase the efficaciousness of orally administered penicillin, and special advantages have been claimed for a variety of adjuvants, e. g., various aluminum salts,[128] calcium carbonate [129] and triisopropanolamine.[130] Information is now available, based on carefully controlled experiments by Bunn and his co-workers [131] and by Finland, Meads and Ory,[132] which indicates not only that there is little to choose among these various adjuvants but also that none has any striking effect in increasing either the height or the duration of penicillin levels in the blood.

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127. Weickhardt, G. G.: Intrathecal Administration of Penicillin in General Paresis, Am. J. Syph., Gonor. & Ven. Dis. **30**:235 (May) 1946.

128. Welch, H.; Price, C. W., and Chandler, V. L.: Prolonged Blood Concentrations After Oral Administration of Modified Penicillin, J. A. M. A. **128**: 845 (July 21) 1945. Paul, W. D.; Rhomberg, C., and Wallace, E.: Penicillin by Mouth in Combination with Aluminum Dihydroxyaminoacetate, J. Indiana M. A. **38**:298 (Sept.) 1945.

129. Seeberg, V. P., and Collen, M. F.: Calcium Carbonate as an Antacid for Oral Penicillin, Science **102**:225 (Aug. 31) 1945.

130. Cutting, W. C.; Halpern, R. M.; Sultan, E. H.; Armstrong, C. D., and Collins, C. L.: Administration of Penicillin by Mouth with Results in the Treatment of Gonorrhea, J. A. M. A. **129**:425 (Oct. 6) 1945.

131. Bunn, P. A.; McDermott, W.; Hadley, S. J., and Carter, A. C.: The Treatment of Pneumococcic Pneumonia with Orally Administered Penicillin, J. A. M. A. **129**:320 (Sept. 29) 1945.

132. Finland, M.; Meads, M., and Ory, E. M.: Oral Penicillin, J. A. M. A. **129**:315 (Sept. 29) 1945.

Bunn's group finds that the height and duration of blood penicillin concentrations observed in fasting serums after oral administration are of the same order of magnitude regardless of whether the penicillin is administered following an antacid, as a suspension in oil, as a suspension in oil mixed with beeswax or in plain water. Also tested were a number of additional vehicles and methods for the oral administration of penicillin, including an oil suspension mixed with shellac, trisodium-citrate tablets, lecithin, mucin, stearates or aluminum hydroxide gel. In no instance was it possible to demonstrate that any method was superior to the oral administration of penicillin in capsule form or dissolved in water. With any of these methods, approximately five times as much penicillin is required to achieve an effective blood concentration when the material is administered by the oral as when it is given by the intramuscular route.

Confirming the findings of Bunn, McDermott and their associates, Finland, Meads and Ory found that an oral dose of 90,000 units of penicillin given one-half hour before breakfast resulted in serum levels comparable with those obtained from 15,000 to 20,000 units given intramuscularly. As compared with serum levels of normal persons, more sustained levels were obtained from oral administration of penicillin, whether given before or after meals, in persons with achlorhydria. The serum levels obtained with ordinary penicillin administered in saline solution were as satisfactory in height and in duration as were those obtained with any of the special preparations for oral administration tested, with the possible exception of the combination of penicillin with aluminum hydroxide gel.

Penicillin levels effective in the treatment of gonorrhea and pneumococcus pneumonia could be fairly well maintained with several oral preparations given every two hours in doses of from 90,000 to 100,000 units. The authors suggest that oral therapy should prove effective in infections in which low doses of parenteral penicillin have proved adequate but that it cannot be expected to be effective against organisms requiring higher doses of penicillin.

McDermott and his co-workers[133] state the belief that the lower concentrations of penicillin which are attained in the blood and urine after oral, as compared with parenteral, administration are chiefly the result of a defect in absorption and not primarily due to penicillin lost by acid destruction. A study of the urinary excretion of penicillin after both oral and intramuscular administration was made in 6 patients with complete achlorhydria. The amount of penicillin excreted ranged from 26 to 100 per cent of the total amount injected intramuscularly

133. McDermott, W.; Bunn, P. A.; Benoit, M.; DuBois, R., and Reynolds, M. E.: The Absorption of Orally Administered Penicillin, Science **103**:359 (March 22) 1946.

and usually was more than 60 per cent. Following oral administration, the range of urinary excretion varied between 8 and 32 per cent. The authors also were able to demonstrate inactivation of penicillin by incubation with emulsions of stool for twenty-four hours.

McDermott's group [134] has further sought to trace the fate of orally administered penicillin to find the reason for its relative ineffectiveness by this route of administration. On the basis of extensive experimentation, they conclude:

1. Absorption of ingested penicillin occurs chiefly from the duodenum. The amount of absorption which occurs from the stomach is not established, but is probably small.

2. Inactivation of penicillin as a result of the acidity of the gastric content is conditioned by a number of variables, and on the whole is seldom great.

3. Absorption of penicillin is rapid. The maximum concentrations are attained in the blood within thirty to sixty minutes of ingestion. The subsequent persistence of penicillin in the blood is a reflection of the height of the maximum concentration orginally attained, and does not appear to be a result of continued absorption from the alimentary tract.

4. Absorption of ingested penicillin is incomplete. Two-thirds or more of an orally administered dose are apparently not absorbed.

5. Once penicillin has passed through the small intestine only insignificant amounts are absorbed.

6. The penicillin in the intestine which is not absorbed is inactivated by the bacteria in the colon, or, if an excess be present, it is excreted in the feces.

7. The necessity for the use of larger amounts of penicillin by the oral than by the intramuscular route is primarily the result of incomplete absorption and cannot be explained satisfactorily on the basis of destruction by acid or bacterial action.

Fortunately, thus far no one has seriously suggested the routine treatment of syphilitic infection with oral administration of penicillin. Any such attempt would be highly inadvisable, being doomed to failure by the frailties of mankind. Few patients can be trusted to take oral medication with sufficient regularity and over such a prolonged period as is necessary to cure syphilis.

In one of the Cornell "Conferences on Therapy," [135] attention is specifically directed toward certain dangers of the abuse of oral administration of penicillin, including the possibility of sensitization of the patient to such a degree that unpleasant reactions may result when more urgent need subsequently arises, and the dangers of self medication.

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134. McDermott, W.; Bunn, P. A.; Benoit, M.; DuBois, R., and Reynolds, M. E.: The Absorption, Excretion and Destruction of Orally Administered Penicillin, J. Clin. Investigation **25**:190 (March) 1946.

135. Conferences on Therapy: Oral Penicillin, New York State J. Med. **46**: 527 (March 1) 1946.

Certainly the increasing use of orally administered penicillin is fraught with grave dangers for patients with syphilis. Self medication and ill advised prescription-authorized oral therapy may well result not only in suppression of the early clinical lesions of syphilis but also in a considerable delay in establishing a diagnosis of syphilis during the period in which the time factor is of greatest importance.

Prolongation of Penicillin Action.

After its parenteral injection in aqueous solution, penicillin is rapidly absorbed and promptly excreted in the urine. If, therefore, therapeutically effective levels are to be maintained in the blood at the site of action, frequently repeated injections are necessary.

Many physicians have sought to prolong the action of parenterally administered penicillin. A complete enumeration of the variously proposed adjuvants and expedients is not within the scope of this review. All of the proposed methods are either absorption delaying or excretion suppressing. Some of the more recently suggested means of delaying absorption include the use of water in oil emulsions,[136] mixtures of penicillin with aluminum and potassium sulfate [137] and simple chilling of the site of injection.[138] Delay in excretion has been attempted by utilization of the antidiuretic effect of ampuls of pitressin [139] and by renal blockage with benzoic acid.[140]

The most successful method of prolonging therapeutically active penicillin levels contiues to be the admixture of calcium penicillin dissolved in peanut oil and beeswax, developed by Romansky and Rittman.[141]

This method has been further studied by its originators [142] and a mixture developed which, after a single intramuscular injection, maintains adequate levels of penicillin in the blood for at least twenty-four

136. Cohn, A., and others: Repository Injections of Penicillin in Water-in-Oil Emulsion: Effect on Gonorrhea, Bull. New York Acad. Med. **21**:442 (Aug.) 1945.

137. Bohls, S. W., and Cook, E. B. M.: The Use of Aluminum-Pencillin Mixtures in Maintenance of Blood Levels of Penicillin: I. Intramuscular Injection of Aluminum-Penicillin, Texas State J. Med. **41**:249 (Sept.) 1945.

138. Trumper, M., and Thompson, G. J.: Prolonging the Effects of Penicillin by Chilling, J. A. M. A. **130**:627 (March 9) 1946.

139. Lich, R., Jr.: A Means of Inducing Oliguresis During Penicillin Administration, J. A. M. A. **128**:1161 (Aug. 18) 1946.

140. Bohls, S. W., and Cook, E. B. M.: The Use of Aluminum-Penicillin Mixtures in Maintenance of Blood Levels of Penicillin: II. Combination of Delayed Absorption by the Use of Aluminum-Penicillin and Renal Blockage with Benzoic Acid, Texas State J. Med. **41**:69 (March) 1946.

141. Romansky, M. J., and Rittman, G. E.: A Method of Prolonging the Action of Penicillin, Science **100**:196 (Sept.) 1944.

142. Romansky, M. J., and Rittman, G. E.: Penicillin Blood Levels for Twenty-Four Hours Following a Single Intramuscular Injection of Calcium Penicillin in Beeswax and Peanut Oil, New England J. Med. **233**:577 (Nov. 15) 1945.

hours and persistent urinary excretion over a period of three days. A relatively constant amount of penicillin is absorbed for each cubic centimeter of penicillin beeswax and peanut oil. Within limits, increase of the size of the injection augments the height of the level of penicillin in the blood and increases the duration of its action. Prolongation of penicillin levels in the blood is accomplished by retardation of absorption by particles of beeswax and is related to the potency of the suspended penicillin in terms of Oxford units per milligram. The preparation found most effectual was one containing 300,000 units in 4.8 per cent beeswax by weight in peanut oil contained in 1 cc. Calcium penicillin in beeswax and peanut oil maintains its potency at least nine months at refrigerator, room and 37 C. temperatures. There was no deterioration after twenty-four hours at 56 C. or after two hours at 100 C.

Atcheson and Edmeades [143] confirms the fact that penicillin is detectable in the blood stream for prolonged periods following its intramuscular injection in beeswax-peanut oil. The finding that penicillin is present in the urine for longer periods than in the blood stream suggested to these authors that penicillin may be clinically available long after its presence in the blood cannot be detected.

Nichols and Haunz [144] also have found penicillin in beeswax-peanut oil mixtures to be a practical and effective method of delaying the absorption of penicillin after intramuscular or subcutaneous injection. At least 0.03 Oxford unit of penicillin was maintained in the blood for at least twenty-four hours following a single intramuscular injection of 300,000 units of calcium penicillin in a 4.8 per cent mixture of beeswax in peanut oil. Penicillin-oil-beeswax mixtures were given subcutaneously to 14 of 40 patients. The remaining 26 received it intramuscularly. Mild inflammation at the site of injection was noted in 2 cases in which the mixture was given subcutaneously. Except for slight local tenderness, no reaction was noted when the mixture was given intramuscularly.

Kirby and his associates [145] have studied the absorption and excretion of penicillin following three hundred and fifty-nine intramuscular and

143. Atcheson, D. W., and Edmeades, D. J.: Blood Levels and Urinary Excretion in Peanut Oil, Beeswax and Penicillin Mixture, Science **102**:199 (Aug. 24) 1945.

144. Nichols, D. R., and Haunz, E. A.: Prolonged Action of Penicillin in Mixtures of Beeswax and Peanut Oil, Proc. Staff Meet., Mayo Clin. **20**:403 (Oct. 31) 1945.

145. Kirby, W. M. M.; Leifer, W.; Martin, S. P.; Rammelkamp, C. H., and Kinsman, J. M.: Intramuscular and Subcutaneous Administration of Penicillin in Beeswax-Peanut Oil, J. A. M. A. **129**:940 (Dec. 1) 1945. Kirby, W. M. M.; Martin, S. P.; Leifer, W., and Kinsman, J. M.: Maintenance of Therapeutic Blood Concentrations of Penicillin for Twenty-Four Hours Following Single Injections of Penicillin-Beeswax-Peanut Oil Mixtures, J. Lab. & Clin. Med. **311**:313 (March) 1946.

subcutaneous injections of a commercial penicillin-beeswax-peanut oil mixture containing 4.8 per cent beeswax and 300,000 units of penicillin per cubic centimeter. There were wide variations in absorption and excretion of penicillin. Assayable levels in the blood persisted for from sixteen to thirty-six hours after intramuscular injection and for from twenty to thirty-six hours following subcutaneous administration. Excretion of penicillin in the urine decreased rapidly after the first twelve hours, but small amounts could be detected for seventy-two hours or more.

In 35 patients treated for syphilis with eight daily administered intramuscular injections of 300,000 units each, penicillin could be assayed in the blood twenty-four hours after each injection on twenty of two hundred and seventy-five occasions, or approximately 7 per cent. Results with subcutaneous administration in 25 patients were superior to those following intramuscular injections, both in uniformity of absorption and in prolongation of blood levels. The authors state the belief that, although larger amounts of penicillin are required than with penicillin in saline solution, penicillin-beeswax-peanut oil mixtures provide an effective and safe method of prolonging the action of the drug in the body.

Penetration of Various Tissues.

Cutting and his associates [146] found that after parenteral administration penicillin is fairly uniformly distributed throughout the body (of rats and rabbits) except to the tissues, such as the central nervous system, which have a high lipid content. The major portion of penicillin administered parenterally was rapidly excreted in the urine and a relatively small amount in the bile and saliva. The fate of a portion of the total amount injected is unknown, but presumably it is destroyed in the body.

Penetration of Body Fluids.—The penetration of penicillin into various body fluids has been studied by Ory and his associates.[116] Cerebrospinal fluid levels were determined in 18 patients receiving penicillin intramuscularly. After injections of 20,000 to 60,000 units, there was no penicillin detectable in the spinal fluids, although blood levels at the time ranged from 0.06 to 0.9 unit per cubic centimeter. After intrathecal injections of 10,000 or 15,000 units, cerebrospinal fluid levels were at twelve hours mostly between 10 and 40 units per cubic centimeter and at twenty-four hours 0.03 to 5.0 units per cubic centimeter. Penicillin levels in pleural fluids, determined in 5 patients two and one-half hours after a single intramuscular injection of 40,000

146. Cutting, W. C.; Luduena, F. P.; Fiese, M.; Elliot, H. W., and Field, J.: Distribution and Fate of Penicillin in the Body, J. Pharmacol. & Exper. Therap. **85**:36 (Sept.) 1945.

units or after an equal amount in divided doses, ranged from 0.03 to 0.22 units per cubic centimeter. Determinations also were made of penicillin concentrations in peritoneal fluid, pericardial fluid and synovial fluid. The results were reasonably comparable one with another and with those for pleural fluid.

Penetration into the Eye.—In studying the penetration of penicillin into the eyes of rabbits, von Sallmann [147] compared the results of subconjunctival injection, iontophoresis and application of cotton packs and found that the highest concentration was obtained in the aqueous humor by iontophoresis and in the cornea and the iris by the prolonged application of cotton packs. The lowest concentration of penicillin in the aqueous humor, the cornea and the iris was observed after subconjunctival injection. Appreciable amounts of penicillin remained in the ocular tissues for about six hours.

Penetration of Amniotic Fluid and Fetal Blood.—Woltz and Zintel [148] have demonstrated that penicillin is present in appreciable amounts in the amniotic fluid and in the fetal blood after the intravenous or intramuscular administration of the sodium salt of the drug to the mother. Concentrations of penicillin in the amniotic fluid were comparable to those of the maternal and fetal circulations.

The Results of Penicillin Therapy.

Early Syphilis.—In the nationwide study of the effects of penicillin in the treatment of syphilis, the major effort of the cooperative study thus far has been to define the usefulness of penicillin in the treatment of early acquired syphilis in adults. From the advent of this program to Aug. 1, 1945, there were 11,589 patients with early syphilis who were treated by the cooperating clinics. Of such importance are the results of this vast and well organized study [149] that its summary is here reproduced:

> The following statements are based on the evidence presented in the body of this report, refer to the treatment schedules analyzed and are to be interpreted with the indicated reservations as to the changing character of penicillin:
>
> I. Evidence of Treatment Failure.—A. *Total Dosage.*—The cumulative percentage failure at the end of eleven months after treatment varied from 15 per cent (2,400,000 units) and 62 per cent (60,000 units).

147. von Sallmann, L.: Penetration of Penicillin into the Eye: Further Studies, Arch. Ophth. **34**:195 (Sept.) 1945.

148. Woltz, J. H. E., and Zintel, H. A.: The Transmission of Penicillin to Amniotic Fluid and Fetal Blood in the Human, Am. J. Obst. & Gynec. **50**:338 (Sept.) 1945.

149. The Treatment of Early Syphilis with Penicillin, Committee on Medical Research and the United States Public Health Service, J. A. M. A. **131**:265 (May 25) 1946.

B. *Combined Drugs.*—The cumulative percentage failure at the end of eleven months with a total dose of 300,000 units was twice as great when it was given alone as when it was given in combination with 320 mg. of arsenoxide (42 per cent versus 21 per cent). This combined dose gave the same results as penicillin alone at a total dosage of 1,200,000 units.

The cumulative percentage failure at the end of four months with 1,200,000 units was twice as great when penicillin was given alone as it was when given with 0.6 to 1.0 Gm. of bismuth (5 per cent versus 2 per cent).

C. *Duration of Disease.*—For long durations of disease the failure rate was higher than for short durations. For a duration of two months or more the failure rate at the end of eleven months was twice that of those treated within the first week of the disease (32 per cent versus 14 per cent).

D. *Color and Sex.*—There was no evidence of a difference between colored and white races by the end of eleven months. The female failure rate was slightly higher than the male.

E. *Reason for Failure.*—The failures were considered by the clinics to be relapses in about 85 per cent and possible reinfections in about 10 per cent. There were no appreciable differences in these proportions for different schedules.

II. Evidence of Seronegativity. A. *Percentage Becoming Seronegative.*—The cumulative percentage becoming seronegative by the end of the seventh month ranged from about 30 for patients receiving less than 60,000 units to about 50 for patients treated with 1,000,000 or more units on three hour seven and one-half day schedules. Patients treated with 300,000 units of penicillin plus 320 mg. of arsenoxide had an accumulated seronegativity rate comparable to that obtained with the highest dosage of penicillin alone.

For patients on three hour three and three-fourths day schedules these findings were reversed. The group receiving 600,000 units had an accumulated percentage seronegativity of 62, while only 24 per cent of patients receiving 2,400,000 units became seronegative by this time. When these rates were made specific for color and sex, the same results were found. The groups did not differ significantly as to duration of disease. They were, however, concentrated in certain clinics.

B. *Clinic Differences for Same Schedules.*—A comparison of different clinics handling the same treatment schedules showed definite differences in the percentage becoming seronegative. It was not possible to test whether this factor accounted for the unexpected results for seronegativity with increasing doses in the three hour three and three-fourths day schedules, since there was no single clinic using all three schedules. In view of the differences in clinic results, it is deemed advisable to compare results on seronegativity for different treatment schedules only if there is a general scattering of clinics involved, or if the results from a single clinic can be compared. Where different schedules are concentrated in a few and different clinics, any comparisons may be misleading, at least until the differences arising from laboratory technics are evaluated.

C. *Duration of Disease.*—For schedule I (2,400,000 units) the percentage becoming seronegative by the end of the seventh month showed a decrease with increasing duration of disease. Those with lesions of at least two weeks' duration before treatment had a cumulative percentage of 70 becoming seronegative by the seventh month after treatment, while those having had the disease for more than eight weeks had a rate of only 38 per cent.

III. Herxheimer Reactions.—The several treatment schedules differed significantly among one another as to both the incidence and the severity of Herxheimer

reactions. Although these differences were noted, there was no clearcut pattern which could be discerned. The results for different schedules could be accurately compared only if these are scattered generally among the various clinics or, alternatively, if the results from a single clinic employing several different schedules are available for analysis.

No serious reactions occurred in patients treated with any of the twelve treatment schedules reviewed.

In comparison with the magnitude of the nationwide cooperative study of penicillin in early syphilis, the experiences of individual investigations seem greatly overshadowed. Reports of small series of cases have, however, been made by Bell,[150] Leifer,[151] Mayne [152] and Schoch and Alexander.[153]

Since the institution of the routine penicillin therapy for early syphilis in the United States Army, thousands of military personnel have been treated with 2,400,000 units in seven and one-half days. According to a recent statement,[154] the failure rate in primary syphilis, including both seronegative and seropositive conditions, has been less than 5 per cent. On the other hand, the failure rate in secondary syphilis has been between 20 and 25 per cent.

In the European Theater of Operations, the results appear to have been more favorable than in the Army as a whole. Here, Pillsbury [155] has evaluated the results of penicillin therapy in 14,000 cases of early syphilis, following the Army-recommended schedule of 2,400,000 units given in sixty intramuscular injections of 40,000 units each at three hour intervals over a period of seven and one-half days. The incidence of clinical relapse is reported as about 1 to 2 per cent, mostly occurring in the first twenty weeks after therapy. The frequency of serologic relapse in seronegative primary syphilis was 1.8 per cent. Penicillin results compare unfavorably in respect to maintenance or achievement of seronegativity with those of intensive arsenobismuth therapy. Data on 792 patients indicate that seronegativity was present six or more months after treatment in 98 per cent of 274 patients with seronegative

150. Bell, N. J.: Penicillin Treatment of Early Syphilis, Rhode Island M. J. **28**:884 (Dec.) 1945.

151. Leifer, W.: The Treatment of Early Syphilis with Penicillin, J. A. M. A. **129**:1247 (Dec. 29) 1945.

152. Mayne, G. O.: Penicillin in One Hundred Cases of Early Syphilis, J. Roy. Army M. Corps **86**:38 (Jan.) 1946.

153. Schoch, A. G., and Alexander, L. J.: Treatment of Early Syphilis with Penicillin, J. A. M. A. **130**:696 (March 16) 1946.

154. Status of Penicillin Treatment of Early Syphilis, Bull. U. S. Army M. Dept. **5**:1 (Jan.) 1946.

155. Pillsbury, D. M.: Penicillin Therapy of Early Syphilis in Fourteen Thousand Patients: Follow-Up Examination of Seven Hundred and Ninety-Two Patients Six or More Months After Treatment, Am. J. Syph., Gonor. & Ven. Dis. **30**:134 (March) 1946.

primary syphilis, 88 per cent of 271 patients with seropositive primary syphilis and 72 per cent of 111 patients with secondary syphilis. The results of examinations of the spinal fluid were available on 642 patients six or more months after completion of therapy. In none had there been clinical neurorecurrence, and in only 3 were there even minimal evidences of activity in the central nervous system.

Pillsbury states the belief that penicillin therapy is decidedly superior to any previous form of treatment in respect to nontoxicity, completion of therapy within a prescribed period, healing of early lesions and control of infectiousness. On only one score was penicillin inferior to intensive arsenobismuth therapy, i. e., the incidence of persistent seropositivity six or more months after treatment.

Marshall [156] has discussed the use of penicillin for early syphilis in the British army. Among 270 patients with early syphilis treated with 2,400,000 units of penicillin for seven and one-half days and followed for six months, the failure rate was 8 per cent, in contrast to a 2 per cent failure rate in an equal number of patients treated by a twenty day schedule of asenoxide and bismuth therapy. Treatment with combined arsenoxide and penicillin also has been used and is believed superior to penicillin alone.

Because of the many gaps in the present knowledge of penicillin therapy, it is not yet possible to outline the optimum method for the use of penicillin in the treatment of early syphilis. Nevertheless, certain minimal suggestions for treatment based on information then available have been advanced.[98]

1. When sodium penicillin in aqueous solution is used for the treatment of syphilis in man, injections should be given by the intramuscular route every two to four hours, preferably every two to three hours, day and night around the clock, for a minimum of seven and one-half to eight days. The presence of penicillin K in commercial penicillin, probably in varying and unpredictable amounts for the next few months [as of June 1946], should be compensated for by an increase in individual and total dosage and if possible by a decrease in the interval between individual injections from three to two hours.

The minimum dose of previously produced and at present available commercial penicillin should be, for seronegative primary syphilis, not less than 3.6 million units (ninety injections of 40,000 units each given every two hours or sixty injections of 60,000 units each given every three hours), and for seropositive primary and early secondary syphilis not less than 5.4 million units (ninety injections of 60,000 units each or sixty injections of 90,000 units each).

For a first relapse (including reinfection, infectious or serologic relapse) of early syphilis after previous treatment of early syphilis this course should be repeated plus 360 mg. of oxophenarsine hydrochloride (mapharsen) or an analogue given twice to three times weekly in six individual intravenous injections of

156. Penicillin Treatment of Syphilis in the British Army, Foreign Letters, J. A. M. A. **130**:963 (April 6) 1946.

60 mg. each plus 1,200 mg. of bismuth subsalicylate given twice weekly in six individual intramuscular injections of 0.2 Gm. each. . . .

For a second relapse of early syphilis after previous penicillin treatment the patient should be transferred from penicillin entirely and placed on metal chemotherapy with arsenic and bismuth, preferably by the twenty-six week schedule employed by the Army and Navy (forty intravenous injections of oxophenarsine hydrochloride and sixteen intramuscular injections of bismuth subsalicylate). . . .

In later stages of syphilitic infection in adult (i. e. latent and late) syphilis the minimum dose should be not less than 3.6 million units, and in certain grave late manifestations of the disease, e. g. dementia paralytica, it should perhaps be as much as 10 million units.

2. In the treatment of infants, and in consideration of the gravity of infantile congenital syphilis, the minimum total dose should probably be greater than that advised for use in adults and should range between a total of 100,000 to 400,000 units per kilogram of body weight. In older children the dosage should be adjusted on a unit for weight basis with a minimum dose of 60,000 units per kilogram of body weight (corresponding to the minimum total of 3.6 million units for an adult).

3. Under no circumstances should penicillin in its at present available form be administered orally for the treatment of syphilis.

4. The only presently satisfactory method of absorption-delaying of penicillin is the administration of calcium penieillin in peanut oil-beeswax. Detailed information is not yet available as to the effects of this preparation in large series of patients with early syphilis or with any other stage of the disease. . . . In any stage of syphilitic infection, the average daily dose for an adult should be 2 cc. (600,000 units) and the total duration of treatment from eight to fifteen days or longer, depending on the stage of the infection. For early syphilis a minimum total dose of 4.8 to 6.0 million units of this preparation is advised.

Calcium penicillin in peanut oil-beeswax should not be administered by the subcutaneous route, since under these circumstances the incidence of sensitizing reactions, with giant urticaria and angioneurotic edema, is excessively high.

5. There is evidence, both from the experimental laboratory and from the clinic, that the addition of arsenic (oxophenarsine hydrochloride) in subcurative dosage to a penicillin treatment schedule enhances the therapeutic effect of each drug. A suggested total dose of an arsenoxide for this purpose is 300 to 360 mg. administered in divided intravenous injections of 40 to 60 mg. each over a total time period of one to four weeks. . . .

In view of [the risks of arsenotherapy] . . . and of possible technical difficulties encountered in the administration of arsenic or in the mere prolongation of treatment necessitated thereby, opinion is divided as to the desirability of including this drug in a recommended penicillin treatment schedule. The majority opinion of a group of competent experts is that the results of penicillin alone, in the dosage and time recommended, would be satisfactory in a sufficiently large proportion of patients with early syphilis treated for the first time to justify eliminating arsenic from the original course of treatment, reserving its use for relapsing cases.

6. There is both clinical and experimental evidence to indicate that an insoluble bismuth salt administered intramuscularly in an oil suspension, e. g. bismuth subsalicylate, produces a slowly absorbed bismuth depot which continually releases small amounts of therapeutically effective bismuth for a period of from three to

six months. There is likewise evidence to indicate that bismuth added to arsenic materially improves the results of metal chemotherapy. If bismuth is added to a penicillin or penicillin-arsenic schedule for early syphilis it may be anticipated that the incidence of infectious relapse within the first six to twelve months after treatment will be materially reduced. This is probably accomplished, for the first few months after treatment, by bismuth effect alone. Later relapse is perhaps prevented or minimized by the fact of development of the patient's own immunity. Whether or not bismuth is of value in effecting cure of the individual patient, it should nevertheless be of considerable aid in minimizing infectious relapse and thereby reducing the risk of spread of infection.

If bismuth is employed, the individual dose should be 0.2 Gm. (expressed as the subsalicylate, not as bismuth metal). A total of 1,000 mg. (five injections) given every other day for a total of nine days is unlikely to produce stomatitis except in patients with extremely bad oral hygiene, or renal damage in patients with previously undamaged kidneys. If the total dose is larger than 1,000 mg., injections should be given not oftener than twice weekly.

However, the opinion of a group of experts is also divided as to the desirability of including bismuth with the original course of penicillin in early syphilis. The majority believe, as for arsenic, that bismuth should be reserved for use in relapsing cases.

7. Commercial penicillin in the dosage and by the methods of administration suggested may be advantageously combined with fever therapy by means of induced tertian malaria in any form of neurosyphilis.

8. The use of sodium penicillin in aqueous solution is a hospital and not an office procedure. Injections of a few hundred thousand units given within one or a few days in a doctor's office are to be avoided.

It should be emphasized that these suggestions for the use of penicillin in syphilis represent a combination of medical desirability and expediency. They are based on information at present available, are only tentative, and are subject to revision within the next few months as further information accumulates.

It is also most vigorously to be emphasized that in the adoption of penicillin therapy for syphilis, the eventual value of which will not be determined for several years to come, the physician has a particular responsibility for careful follow-up and frequently repeated post-treatment observation on all patients so treated.

Acute Syphilitic Nephrosis.

Holman and Makovsky [157] report the successful treatment of acute syphilitic nephrosis with penicillin. Tucker [158] also has found penicillin dramatically efficacious in the treatment of secondary syphilis complicated by acute nephrosis and iritis. Being nontoxic to the kidney, penicillin is preferred to metal chemotherapy, which may further damage the renal parenchyma. Barr and his associates [159] also have successfully treated

157. Holman, D. V., and Makovsky, I. H.: Acute Syphilitic Nephroses Treated with Penicillin, New York State J. Med. **46**:520 (March 1) 1946.

158. Tucker, H. A.: Penicillin Treatment of Acute Syphilitic Nephrosis and Iritis, Am. J. M. Sc. **211**:718 (June) 1946.

159. Barr, J. H.; Cole, H. N.; Driver, J. R.; Leas, R. D.; Miller, M., and Strauss, L. G.: Acute Syphilitic Nephrosis Successfully Treated with Penicillin, J. A. M. A. **131**:741 (June 29) 1946.

acute syphilitic nephrosis with penicillin, and they agree that this is the ideal form of therapy, since there have been no reports of renal irritation from its use.

Penicillin Therapy of Neurosyphilis.

Penicillin has also been widely used in cases of syphilis of the central nervous system. The results of therapy in neurosyphilis, as observed in the several cooperating clinics, do not lend themselves readily to amalgamation. So insusceptible of definition are "improvement" and "progression" in cases of neurosyphilis and so widely do clinicians vary in their interpretations of the clinical phenomena involved that no attempt has been made to consolidate reports. Data are available, however, from several of the clinics that have participated in the nationwide study of penicillin in neurosyphilis.

Rose and his co-workers [160] at the Boston Psychopathic Hospital have treated 106 neurosyphilitic patients with penicillin. The majority of the patients also were given concomitant fever therapy, either by inoculation malaria or by fever cabinet, in amounts approximately half that generally considered sufficient. The total dosage of penicillin used was 3,000,000 units (50,000 units per injection for a total of sixty injections). Their report summarizes the outcome in 70 cases followed from four to twelve months. Clinically, 28 of the 70 patients were improved, 37 were essentially unchanged and 5 were worse. The greatest percentage of clinical improvement was noted among the 49 patients with dementia paralytica. The early results of therapy also were striking in primary optic atrophy, since in 5 of their 6 patients with this ocular condition further loss of vision appeared to have been prevented. Repeated examinations of the cerebrospinal fluid revealed a prompt response of elevated cell counts and total protein determinations in most of the previously untreated patients and a more gradual reduction of the Wassermann titer.

An attempt was made to compare the results of therapy with penicillin plus suboptimal fever therapy with those of "adequate" fever followed by arsenical chemotherapy. The comparison suggests that there is little to choose between in the two methods of treatment. The relative safety and the less prolonged periods required recommend the newer form of therapy. Enjoining caution in the interpretation of their results, the authors conservatively conclude merely that penicillin "is an effective therapeutic agent for late neurosyphilis." Their study, however, suggests that the combination of penicillin with short courses

160. Rose, A. S.; Trevett, L. D.; Hindle, J. A.; Prout, C., and Solomon, H. C.: Penicillin Treatment of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **29**:487 (Sept.) 1945.

of fever therapy may significantly improve the prognosis of the patients formerly considered unsuitable for full courses of fever therapy.

At the Mayo Clinic, 100 patients with various types of neurosyphilis have been treated with penicillin. O'Leary, Brunsting and Ockuly [161] summarize the results unenthusiastically as follows:

1. The outstanding result common to most of the patients in this series following the use of penicillin was a return of the cell count, protein and gold curve to within normal limits in the studies of the cerebrospinal fluid with reduction of the strength of the complement fixation and titer reactions of the blood.

2. The outstanding clinical effects as noted among patients who had objective and subjective signs of neurosyphilis were a gain of weight and a reduction of severity and frequency of the pains in the legs. The early symptoms of dementia paralytica were not influenced.

3. The patients who had meningeal neurosyphilis were most responsive both clinically and serologically, while patients who had the parenchymatous forms of the disease were helped only slightly if at all.

4. The outstanding serologic results noted were among the patients who had asymptomatic neurosyphilis and who received penicillin intravenously in doses approximating 1,200,000 units in a week, in association with either three spinal drainages or intraspinal treatments (Swift-Ellis type).

5. Penicillin given in combination with fever therapy, either malarial or by means of the fever machine, did not improve the clinical results noted from fever treatment alone.

6. The administration of penicillin by the intravenous, intramuscular or intraspinal route, alone or in combination with fever therapy, both malarial and by machine, leads us to believe that penicillin alone is not capable of controlling the parenchymatous forms of neurosyphilis. However, in cases of meningeal forms of the disease and in those in which there was a high degree of pleocytosis in association with asymptomatic neurosyphilis, the results thus far are encouraging.

7. In occasional cases of neurosyphilis penicillin therapy produces clinical and serologic results that are outstanding. However, these favorable results are noted in only a few cases and often appear when least expected. It is not possible at this time to account for such great therapeutic discrepancies.

Callaway's group [162] has recorded observations on the first 100 patients with neurosyphilis they have treated with penicillin. Classified according to clinical manifestations, there were 37 patients with asymptomatic neurosyphilis, 39 with dementia paralytica, 11 with tabes dorsalis, 7 with tabetic dementia paralytica and 6 with diffuse meningovascular neurosyphilis. All, regardless of type of neurosyphilis, were treated with a total of 4,000,000 units of penicillin given intramuscularly in divided doses. Preliminary observations after at least six months'

161. O'Leary, P. A.; Brunsting, L. A., and Ockuly, O.: Penicillin in the Treatment of Neurosyphilis, J. A. M. A. **130**:698 (March 16) 1946.

162. Callaway, J. L.; Noojin, R. O.; Flower, A. H., Jr.; Kuhn, B. H., and Riley, K. A.: The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, Am. J. Syph., Gonor. & Ven. Dis. **30**:110 (March) 1946.

follow-up indicate that 60 per cent of this series of patients have shown clinical improvement plus definite improvement in abnormalities of the spinal fluid; 31 per cent, clinical improvement only; 4 per cent, improvement in cerebrospinal fluid unassociated with clinical changes, and 5 per cent, both clinical progression and lack of improvement in the cerebrospinal fluid. Among the 39 patients with dementia paralytica, 22 (56 per cent) were improved both clinically and in respect to abnormalities of the spinal fluid. Of 18 with tabes dorsalis or tabetic dementia paralytica 1 became worse, 5 were unchanged, 5 slightly improved, 8 moderately improved and 7 had complete remissions. Four of 6 patients with syphilis classed as "meningovascular" responded in excellent fashion, and the other 2 also improved. Febrile Herxheimer reactions were frequent, but there were no reactions severe enough to necessitate termination of penicillin therapy.

The results, these workers believe, compare not unfavorably with the early response to fever therapy and are superior to those obtained with the more prolonged, more expensive and more dangerous metal chemotherapy.

A summation of the effects of penicillin alone in the treatment of 283 patients with neurosyphilis at the University of Pennsylvania has been made by Stokes and Steiger.[163] The most striking effects they observed were on the abnormalities in the cerebrospinal fluid, in which definite improvement was noted in 74 per cent of the patients treated. Improvement in the spinal fluid occurred in 62 per cent of the patients treated for dementia paralytica, 57 per cent of the patients with tabes dorsalis, 60 per cent of the patients with asymptomatic involvement of the central nervous system and 63 per cent of the patients with congenital neurosyphilis. In only 6 patients in the entire series did the spinal fluid become worse. Over-all clinical improvement of some degree occurred in 65 per cent of the patients with symptomatic neurosyphilis, 24 per cent improving decidedly and 41 per cent slightly. Nine per cent of the patients were worse from a clinical viewpoint. Definite improvement is claimed for 30 per cent of patients with dementia paralytica, 31 per cent of those with tabes dorsalis and 17 per cent of those with meningovascular neurosyphilis. The results with primary optic atrophy were inconclusive, but in 2 of 5 cases gastric crises were ameliorated. The disability resulting from Charcot's joints was, as might be expected, unchanged. In the authors' experience, the maximum effect of therapy was manifest within four months, although improvement and ultimate normality occasionally followed an unsatisfactory or atypical early trend.

163. Stokes, J. H., and Steiger, H. P.: Penicillin Alone in Neurosyphilis, J. A. M. A. **131**:1 (May 4) 1946.

Dementia Paralytica.—In Doty, Koteen and McDermott's [164] series of 115 neurosyphilitic patients treated with penicillin, there were 8 with dementia paralytica. Satisfactory therapeutic results were observed in 4 of these 8 patients during a follow-up period of six to twelve months. With one exception, the observed improvement was not so striking as usually is seen at a comparable interval after malarial therapy. Two patients with advanced paresis failed to improve after 9,000,000 and 19,000,000 units of penicillin respectively. These authors state the belief that although penicillin exerts a definitely beneficial effect on the mental, physical and laboratory abnormalities of dementia paralytica the extent of this beneficial effect, at least with the dosage used, is not so satisfactory as that following inoculation malaria.

Rosanoff and Norman [165] report results of penicillin treatment in 2 cases of dementia paralytica. The observations are unusually complete, including a battery of psychologic studies, such as the Hartford deterioration and Rorschach tests, as well as pretreatment and post-treatment electroencephalograms. One of their patients received 3,000,000 units of penicillin and was followed ten months; the other received 1,080,000 units and was observed over a period of five months. In both there was definite clinical and laboratory evidence of arrest of the infectious process. The "mental age" of both patients improved after penicillin therapy, and electroencephalographic abnormalities completely disappeared in 1 of the 2 patients treated. Improvement in the observed abnormalities in the cerebrospinal fluid was also evident.

Stern and Campbell [166] also have found repeated psychologic tests of value in evaluating the response of patients with dementia paralytica to therapy with penicillin and suggest the use of the adult scale for measurement of intelligence and the Rorschach test to reveal abnormalities of the personality.

Jones and Perk [167] report 6 patients with dementia paralytica treated with penicillin (two courses, each of 2,400,000 units, separated by one month). In all cases, improvement in the abnormalities of the spinal fluid occurred, reduction in the cell count being the promptest and most consistent change. Mental changes were assessed by repeated psychometric tests (Raven's progressive matrices, Shipley-Hartford retreat

164. Doty, E. J.; Koteen, H., and McDermott, W.: The Clinical Responses in General Paresis to Treatment with Penicillin, Bull. New York Acad. Med. **21**:434 (Aug.) 1945.

165. Rosanoff, W. R., and Norman, J. K.: Report of Two Cases of Paresis Treated with Penicillin, South. M. J. **38**:819 (Dec.) 1945.

166. Stern, J. E., and Campbell, H. M.: Early Effects of Penicillin Treatment of Dementia Paralytica, Arch. Neurol. & Psychiat. **55**:266 (March) 1946.

167. Jones, W. L., and Perk, D.: The Early Results of Penicillin in G. P. I., J. Ment. Sc. **92**:414 (April) 1946.

scale and the Wechsler-Bellevue intelligence scale). Three patients were improved mentally, 1 was unchanged and 2 became progressively worse.

Acute Syphilitic Meningitis.—Nelson and Moore[168] report additional information concerning a group of 10 previously reported patients with acute syphilitic meningitis treated with penicillin. The remarkable feature of the additional year of observation is that in all 10 patients the reactions of the spinal fluids, originally strongly positive, had become entirely negative. In none had there developed any clinical evidence of neurosyphilis, 1 had had an infectious relapse and serologic reactions of the blood had reverted to negative in 6 of the 10 cases. These results are believed superior to those obtainable with metal chemotherapy in a comparable period. In view of their excellent results with penicillin given intramuscularly, the authors see no necessity for intrathecal administration in cases of acute syphilitic meningitis.

Arachnoiditis with Subarachnoid Block.—In the series of neurosyphilitic patients being treated with penicillin by Callaway and his associates,[169] there have been 2 cases of syphilitic arachnoiditis with subarachnoid block. In contrast to the unfavorable results that have in the past followed the use of other forms of antisyphilitic therapy, definite improvement occurred subsequent to the administration of 4,000,000 units of penicillin.

Erb's Spastic Paraplegia.—As with all previous forms of therapy, penicillin appears, from the report of Tucker,[170] not to offer any real hope to patients with Erb's spastic paraplegia. Two patients who received 3,760,000 and 6,560,000 units of penicillin respectively were unimproved or worse after therapy. Another died of Clostridium welchii infection one hundred and ninty-nine days after the first of two courses of 4,000,000 units of penicillin, postmortem examination revealing anterolateral degeneration of the spinal cord, most extreme in the corticospinal tracts. A fourth patient received 10,000,000 units of penicillin concomitantly with malarial fever therapy, with no beneficial effect evident within an observation period of one hundred and twenty-one days. Although admitting that the reported series is small and the duration of post-treatment observation relatively short, the author feels justified in his pessimistic conclusion that commercial penicillin, at least

168. Nelson, R. A., and Moore, J. E.: Acute Syphilitic Meningitis Treated with Penicillin: A Progress Report, Am. J. Syph., Gonor. & Ven. Dis. **30**:227 (May) 1946.

169. Callaway, J. L.; Noojin, R. O.; Kuhn, B. H.; Riley, K. A., and Segerson, J. A.: Syphilitic Arachnoiditis Treated with Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **30**:231 (May) 1946.

170. Tucker, H. A.: Penicillin Treatment of Erb's Syphilitic Spinal Spastic Paraplegia, Bull. Johns Hopkins Hosp. **78**:161 (April) 1946.

in the amounts employed, does not cure nor even arrest the process of this syndrome.

Electroencephalograms before and after Penicillin Therapy.—Callaway and his co-workers [171] have studied the electroencephalograms of 38 patients with neurosyphilis before and after penicillin therapy. Their findings agree with previous reports in that no correlation was found between the severity of neurosyphilis and presence or absence of electroencephalographic abnormalities. After penicillin therapy (4,000,000 units in ten days), many formerly abnormal tracings became normal. There was no strict correlation between the clinical results of treatment and improvement in the electroencephalograms. Abnormal electroencephalograms in neurosyphilis are interpreted as the consequences of local cerebral anoxia and of generalized or localized cerebral inflammation. Many of these abnormalities apparently are reversible with penicillin therapy. The authors express the opinion that electroencephalographic tracings are a valuable adjunct in determining the effect of penicillin in the treatment of syphilis of the central nervous system.

Penicillin in Benign Late Syphilis.

Proof that the lesions of benign late syphilis respond to penicillin therapy has been submitted by Dexter and Tucker,[172] who have studied 21 patients with benign late gummatous syphilis. In 18 cases, cutaneous, mucocutaneous or mucosal gummas were present; 4 of the patients had osseous lesions, and 2 had gumma of the liver. The clinical response was uniformly favorable. Cutaneous and mucosal gummas underwent rapid and progressive improvement after penicillin therapy, there being only 1 patient with incipient relapse and 1 with failure of treatment in the entire group. The lesions of both of these 2 patients healed completely after a second and more intensive course of penicillin. Late syphilitic lesions of the skeleton and of the liver appeared to respond favorably.

Penicillin in Cardiovascular Syphilis.

Evaluation of the usefulness of any therapeutic agent in cardiovascular syphilis involves many years of observation. There is, therefore, no information as to the results of penicillin therapy in this late manifestation of the disease. Many writers have cautioned against the use of large doses of penicillin in the presence of cardiovascular syphilis, fearing possible Herxheimer reactions.

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171. Callaway, J. L.; Löwenbach, H.; Noojin, R. O.; Kuhn, B. H., and Riley, K. A.: Electroencephalographic Findings in Central Nervous System Syphilis Before and After Treatment with Penicillin, J. A. M. A. **129**:938 (Dec. 1) 1945.

172. Dexter, D. D., and Tucker, H. A.: Penicillin Treatment of Benign Late Gummatous Syphilis: A Report of Twenty-One Cases, Am. J. Syph., Gonor. & Ven. Dis. **30**:211 (May) 1946.

Dolkart and Schwemlein [173] report that in 2 patients with cardiovascular syphilis treated with penicillin there developed untoward symptoms (precordial pain, cardiac consciousness and premature systoles) so severe that discontinuation of therapy seemed to them advisable. Whether these were true Herxheimer reactions is questionable.

Penicillin in the Prevention of Prenatal Syphilis.

In the prevention of prenatal syphilis, penicillin has proved spectacularly successful. All writers are agreed that it is a convenient, safe and effective form of therapy.

A report by Ingraham and his associates [174] deals with 49 pregnant women, of whom, at the time of treatment, 26 had manifest early, 19 early latent, 3 late latent and 1 congenital syphilis. Specific therapy during the pregnancy was with penicillin alone, 10 patients receiving a total of 1,200,000 units and 30 a total of 2,400,000 units. The sodium salt was used in all cases, and injections were given intramuscularly at intervals of three to four hours over a minimum of seven days.

At the time of writing, 1 syphilitic infant had been born from among thirty-seven pregnancies which had gone to term, a "degree of success equal to if not greater than that obtained with the arsenical-bismuth regimens at present widely employed." The mother of the baby born with congenital syphilis had been given 1,200,000 units of penicillin for secondary syphilis during the fifth month of pregnancy. Clinical relapse occurred in the mother during the last month, and dark field–positive lesions were present at the time of delivery.

In these authors' experience, the possibility of abortion seemed a definite threat to some pregnant syphilitic women treated with penicillin. They state the belief that this threat may be anticipated and that it may be avoided by reduction of initial doses for forty-eight hours, rest in bed, sedation and temporary cessation of penicillin therapy if signs of threatened abortion are noted.

So successful has the penicillin treatment of pregnant women been in the hands of Goodwin and Moore [175] that they recommend that metal chemotherapy for syphilitic mothers be abandoned and penicillin adopted in its stead. Their series of 33 infants born to 31 mothers treated with penicillin alone for early syphilis includes no infants with prenatal syphilis. They do not concur in the belief that pregnancy exerts any effect in delaying the serologic response. Neither do they share in the

173. Dolkart, R. E., and Schwemlein, G. X.: The Treatment of Cardiovascular Syphilis with Penicillin, J. A. M. A. **129**:515 (Oct. 13) 1945.

174. Ingraham, N. R., Jr.; Stokes, J. H.; Beerman, H.; Lentz, J. W., and Wammock, V. S.: Penicillin Treatment of the Syphilitic Pregnant Woman, J. A. M. A. **130**:683 (March 16) 1946.

175. Goodwin, M. S., and Moore, J. E.: Penicillin in Prevention of Prenatal Syphilis, J. A. M. A. **130**:688 (March 16) 1946.

opinions that abortion is a frequent evidence of therapeutic shock or that great initial caution in treatment is necessary to prevent this untoward reaction. They summarize:

1. The total dose of penicillin should be not less than 2.4 million units administered intramuscularly in aqueous or saline solution at intervals of not less than two nor more than three hours night and day.

2. The total duration of treatment should be not less than seven and one-half days. . . .

4. Following completion of penicillin treatment, the mother must be followed clinically and with quantitatively titered serologic tests at least as often as once a month until delivery (and preferably for the first year after treatment) and at appropriate intervals thereafter.

5. Retreatment with penicillin should be given during pregnancy to the mother if (*a*) there is evidence of clinical or serologic relapse or (*b*) the original maternal serologic titer does not significantly decline within three months after treatment.

6. The infant must be followed after birth for a minimum period of three months by means of (*a*) frequently repeated physical inspections, (*b*) quantitatively titered blood serologic tests, preferably every two weeks, and (*c*) roentgenograms of the long bones taken preferably at the first six weeks of life.

7. There is no satisfactory evidence that abortion, actual or threatened, is more frequent during penicillin treatment of the mother than during other forms of antisyphilitic treatment, or indeed more frequent than the expected incidence of spontaneous abortion in normal women. . . .

8. It is not yet determined whether a woman with early syphilis, treated with penicillin while nonpregnant or during an earlier pregnancy, may be permitted to go through a subsequent pregnancy without treatment. Although 3 women in the present series have delivered normal children in a second pregnancy in which no treatment was given, further experience must accumulate before the point can be decided. Pending further information, a pregnant syphilitic woman previously treated with penicillin, and whether or not this earlier treatment was apparently successful as to the mother's infection, should be retreated with penicillin in each succeeding pregnancy.

Combining in summary the material from the Pennsylvania group and the group from Johns Hopkins University, Goodwin and Moore state:

1. Fifty-seven pregnant women with early syphilis have been treated with penicillin in two university clinics. Sixty infants have been born [alive] to these women . . . only 1 has developed clinical or laboratory evidence of congenital syphilis. In this 1 case, syphilis in the child might possibly have been prevented. The remaining 59 infants are all apparently normal, and 42 of these have been followed for a long enough time after birth to make practically certain of the diagnosis of "no syphilis."

2. These results in the prevention of prenatal syphilis are superior to any heretofore attainable with any method of treatment. . . .

4. It is recommended that in syphilitic pregnant women penicillin be used routinely for the prevention of prenatal syphilis, other methods of treatment being abandoned.

In further reference to the alleged effects of penicillin on uterine activity, Leavitt [176] has reported that among 21 pregnant women treated with penicillin there were 8 who had uterine cramps or bleeding and that 2 of these patients aborted. He also notes that among 206 nonpregnant women there were 17 who began to menstruate during the first day of penicillin therapy.

Speiser and Thomas,[177] however, were unable to find any conclusive evidence of unusual effects of penicillin on the uterus in their review of 156 patients with prenatal syphilis treated at Bellevue Hospital. They also record having given penicillin to over 1,300 women without noting any menstrual abnormality which could be attributed to the effects of therapy. The menstrual cycles of 100 women under treatment for early syphilis with penicillin subsequently were carefully studied, and in only 1 instance was there any alteration from the usual cycle.

Penicillin Therapy of Congenital Syphilis.

Information as to the effectiveness of penicillin therapy in congenital syphilis has accumulated slowly. A preliminary report has been made by Wilkinson, Saunders and Hansen [178] on the results of penicillin therapy in 29 infants and children with congenital syphilis. The doses used were 20,000 to 40,000 units per kilogram given as sixty to eighty divided doses over seven and one-half to ten days. In 13 infants with manifest lesions, the clinical results were satisfactory: cutaneous lesions improved within twenty-four to forty-eight hours and were healed by the time treatment was completed; rhinitis persisted for two to four weeks; osseous lesions healed slowly, and serologic titers decreased progressively. Of 4 children with asymptomatic early congenital syphilis, satisfactory serologic response occurred in 3 following treatment. In late congenital syphilis, penicillin appeared of value in 4 of 6 patients with interstitial keratitis.

Ingraham and the Philadelphia group [179] have treated with penicillin 26 infants with early congenital syphilis. The average age of these children was 3.6 months. All had clinical manifestations of the disease. The dosage of penicillin used was at first comparable to approximately 2,400,000 units for a 150 pound (68 Kg.) adult. Later this dosage was substantially increased. In general, the clinical response was good.

176. Leavitt, H. M.: Clinical Action of Penicillin on the Uterus, J. Ven. Dis. Inform. **26**:150 (July) 1945.

177. Speiser, M. D., and Thomas, E. W.: Regarding the Unusual Effect of Penicillin Therapy upon the Uterus, J. Ven. Dis. Inform. **27**:20 (Jan.) 1946.

178. Wilkinson, E. E.; Saunders, W. H., and Hansen, A. E.: Penicillin in the Treatment of Congenital Syphilis, Texas State J. Med. **41**:401 (Dec.) 1945.

179. Ingraham, N. R., Jr.; Stokes, J. H.; Beerman, H.; Lentz, J. W.; György, P., and Rose, E. K.: Penicillin in the Treatment of the Syphilitic Infant, J. A. M. A. **130**:694 (March 16) 1946.

Symptoms and signs of syphilitic infection were noted to improve and abnormal roentgenologic findings seen gradually to regress over a period of months. Of the infants who remained under observation for longer than six months after treatment, 10 (71 per cent) remained clinically normal and were seronegative and 4 were clinically well but still seropositive. In 40 per cent of the infants there developed, in addition to a febrile reaction, symptoms of severe gastrointestinal disturbance. This consisted in abdominal distention, anorexia, diarrhea and occasionally vomiting. In some of the infants these symptoms were present on admission, but almost uniformly they were accentuated after penicillin was started, tending to regress as the therapy was completed. There were 5 infants who died, none of the deaths being attributed by the authors to penicillin. Intercurrent infection superimposed on debility and toxemia from systemic syphilis was the usual cause of death. The paramount importance of expert pediatric attention is stressed. The authors state the belief that larger doses of penicillin given over a longer period will result in a greater proportion of favorable results.

Having observed 22 congenitally syphilitic infants treated with penicillin, Heyman and Yampolsky [180] note that 13 became clinically and serologically well within a period of eighteen months. Four others had persistently positive serologic reactions sixteen months after treatment. There were three deaths in this series and two serologic and cerebrospinal fluid relapses. All deaths occurred in patients with severe infections, and the authors express the opinion that the greatest considerations in the prevention of fatality are adequate nutrition, hydration and the prevention of intercurrent infections.

Neilson and his collaborators [181] have treated 39 syphilitic infants and children with penicillin. Of patients in the 23 cases followed from two to sixteen months, 7 were clinically well and seronegative, 6 were clinically well and seropositive in low titer and 10 remained well but persistently strongly seropositive. One fatality occurred, the cause of death being undetermined. In 3 cases, syphilitic periostitis disappeared clinically in approximately one month and serial roentgengraphic studies showed complete healing in three months. There was definite improvement in the child's nutritional state during and after penicillin therapy.

The Effect on the Evolution of Syphilis of Small Doses of Penicillin

The widespread use of penicillin in the treatment of gonorrhea has raised several problems with respect to the effect of such therapy on

180. Heyman, A., and Yampolsky, J.: Treatment of Infantile Congenital Syphilis with Penicillin, Am. J. Dis. Child. **71**:506 (May) 1946.

181. Neilson, A. W.; Chard, F. H.; Klingberg, W. G.; Hanchett, L. J.; Gabby, W. H.; Rodriguez, J., and Watkins, C.: Treatment of Congenital and of Acquired Syphilis in Infants and in Children by Penicillin, Arch. Dermat. & Syph. **53**:625 (June) 1946.

concomitantly acquired syphilis. Since the doses of penicillin usually employed (100,000 to 200,000 units) are sufficient to cause the disappearance of T. pallidum from primary lesions previously dark field positive but are subcurative for established syphilis in human beings, it is conceivable that such therapy given during the incubation period of syphilis may delay the appearance of the early lesions, suppress all outward manifestations and result in asymptomatic infection or actually abort the disease. MacKenzie and Wrong [182] suggest that there also may be delay in the appearance of reagin in the blood, an atypical appearance of the primary lesion and difficulty in obtaining positive results on dark field examinations.

At least some of these possibilities appear to have been realized in clinical practice. Leifer and Martin,[183] for example, found that of 15 patients treated with penicillin for gonorrhea while suffering from simultaneously acquired syphilitic infection penicillin appeared to prolong the incubation period of primary syphilis in 3 and to suppress the early lesions in 8. Derzavis and Bond [184] also have observed that the early lesions of syphilis may be suppressed by small doses of penicillin.

A review of the published reports of cases pertinent to a consideration of the effect of the penicillin treatment for gonorrhea administered during the incubation period of syphilis has been made by Walker and Barton.[185] These authors indicate the danger to the person and to public health of unrecognized syphilitic infections in patients receiving penicillin therapy for gonorrhea and stress the importance of serologic follow-up. In the presence of "reasonable suspicion of co-existing syphilis," it is suggested that penicillin therapy be withheld until a definite diagnosis of the latter disease can be either established or excluded.

The frequency of febrile Herxheimer reactions following the penicillin treatment of syphilis has suggested to Bauer and Egolf [186] that patients being treated for gonorrhea with penicillin in whom there develop reactions such as fever, headache and malaise should be suspected of having a systemic Herxheimer reaction due to unsuspected syphilis. Walker and Barton [185] and Leifer and Martin [183] attest the validity of this observation.

182. MacKenzie, D. J., and Wrong, N. M.: Some Aspects of Penicillin Therapy in Early Syphilis, Canad. M. A. J. **54**:443 (May) 1946.

183. Leifer, W., and Martin, S. P.: Effect of Penicillin on Course of Early Syphilis, J. A. M. A. **130**:203 (Jan. 26) 1946.

184. Derzavis, J. L., and Bond, F. T.: Suppression of Early Syphilis by Subtherapeutic Dosage of Penicillin: Report of a Case, U. S. Nav. M. Bull. **46**:259 (Feb.) 1946.

185. Walker, A. E., and Barton, R. L.: The Treatment of Gonorrhea with Penicillin During the Incubation Period or Early Phase of Syphilis: A Review, J. Ven. Dis. Inform. **26**:241 (Nov.) 1945

186. Bauer, F. K., and Egolf, C. F.: Herxheimer Syndrome Following Penicillin in Unsuspected Syphilis, Bull. U. S. Army M. Dept. **4**:239 (Aug.) 1945.

Minimizing the effects of small doses of penicillin (such as those used in the treatment of gonorrhea) on the evolution of syphilis, Cronin [187] points out that it is difficult to prove absence of secondary exposures between the time of the penicillin therapy of gonorrhea and the appearance of the syphilitic lesion and a sexual exposure sufficiently remote in time from any previous exposure so as to render it the probable source of the double infection.

The problem has been approached experimentally by Magnuson and Eagle.[188] These investigators were able to show that small doses of penicillin administered to rabbits at varying intervals during the incubation period of syphilis may either delay the appearance of the primary lesion or actually abort the infection. In general, the smaller the inoculum and the earlier treatment was begun, the greater was the proportion of lesions that failed to develop. The authors summarize their study as follows:

1. The evolution of early syphilitic infection in rabbits was materially modified by the administration during the incubation period of small doses of penicillin comparable to those used in the treatment of gonorrhea in man.

2. Four hundred units per kilogram injected intramuscularly five times at three-hour intervals to a total of 2,000 units per kilogram, a dose which was less than 1/32 of the amount, similarly administered, necessary to cure an established syphilitic infection in rabbits, either aborted the infection entirely, or significantly prolonged the incubation period.

3. In general, the smaller the inoculum, and the earlier penicillin was administered during the incubation period, the larger was the proportion of lesions completely suppressed, rather than merely retarded.

4. While no asymptomatic infections were observed in the present experiments, many of the delayed lesions were so small that comparable lesions in man might well have escaped detection, resulting in infections "asymptomatic" in effect if not in fact.

5. With the increasing use of penicillin as a primary therapeutic measure in gonorrhea, it is probable that the number of aborted, delayed, or "asymptomatically" acquired syphilitic infections will increase. Patients receiving penicillin treatment for gonorrhea should be kept under close serologic and clinical observation for a period of at least four months and preferably longer to guard against the latter two possibilities.

Untoward Reactions of Penicillin.

Penicillin is a relatively innocuous substance. Reports of untoward reactions following its use have been confined almost exclusively to

187. Cronin, E.: Coincidental Syphilis and Gonorrhea, Brit. J. Ven. Dis. **21**:135 (Sept.) 1945.

188. Magnuson, H. J., and Eagle, H.: The Retardation and Suppression of Experimental Early Syphilis by Small Doses of Penicillin Comparable to Those Used in the Treatment of Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **29**:587 (Nov.) 1945.

allergic manifestations in the skin. The allergic reactions reported include: (1) urticaria or angioneurotic edema; (2) papular, vesicular or bullous eruptions, sometimes followed by desquamation; (3) contact dermatitis; (4) an Arthus type of response following repeated intradermal injections; (5) a tuberculin-like sensitivity of the skin, and (6) delayed reactions similar to "serum sickness."

Serious reactions were encountered in about 0.5 per cent of the patients treated by Cormia, Jacobsen and Smith.[189] According to these writers, reactions may occur shortly after the institution of therapy, as a result of a preexisting hypersensitivity, or at later intervals, because of developing sensitization. Both early and late reactions may be so serious as to require discontinuation of therapy. Intradermal testing with penicillin is of limited value as an aid to diagnosis and as a guide to further treatment.

The untoward reactions encountered in 124 patients treated with sodium penicillin have been analyzed by Kolodny and Denhoff.[190] Of the total number of patients, approximately 16 per cent had immediate and 7 per cent delayed reactions. No significant realtionship was found between the incidence of reactions and previous penicillin therapy. There was no correlation between a past history of personal or familial allergies, previous cutaneous disease, drug intolerance, previous penicillin therapy or reaction referable to it and the incidence of reaction.

Lamb[191] has reported the exacerbation of eruptions considered to be epidermophytosis of the feet and tinea cruris during the administration of penicillin. He concludes that this is "due to allergy" from the drug but does not discuss in sufficient detail the possibility that the reaction may depend on the exacerbation of a preexisting fungous infection.

The incidence of delayed "serum sickness" reactions to penicillin is small. According to Gordon,[192] it occurs probably not oftener than 1:1,500 or 1:2,000 in patients treated with penicillin. Characteristic features of 3 cases reported were delay in appearance, fever and tachycardia, severe urticaria, arthralgia and hydrarthrosis, exfoliative dermatitis of the palms of the hands and a self-limited course of seven to ten days. Anaphylactic sensitization in susceptible persons by the penicillin fraction itself is considered to be the cause of this allergic manifestation.

189. Cormia, F. E.; Jacobsen, L. Y., and Smith, E. L.: Reactions to Penicillin, Bull. U. S. Army M. Dept. **4**:694 (Dec.) 1945.

190. Kolodny, M. H., and Denhoff, E.: Reactions in Penicillin Therapy, J. A. M. A. **130**:1058 (April 20) 1946.

191. Lamb, J. H.: Allergic Reactions During the Administration of Penicillin, Arch. Dermat. & Syph. **52**:93 (Aug.) 1945.

192. Gordon, E. J.: Delayed Serum Sickness Reaction to Penicillin, J. A. M. A. **131**:727 (June 29) 1946.

An editorial writer,[193] commenting on the allergic reactions to penicillin, concludes:

> Almost all of the reports [of allergic responses to penicillin therapy] . . . lack, in one respect or another, the essential details to provide a complete picture of the source and mechanism of penicillin allergy. The source of the allergen has not been satisfactorily determined. Presumably, it may arise from its presence in the Penicillium fungus, in the media, in the chemicals added in the preparation of penicillin, in the interaction between the chemicals and intermediary products, and in the penicillin itself. No concerted attempt has been made to localize the source of this allergen. . . . More complete immunologic investigation of the allergic patients and more extensive animal experimentation are needed to solve the problem of the origin and mechanism of allergy to penicillin.

THE SYNERGISTIC ACTION OF PENICILLIN AND OXOPHENARSINE HYDROCHLORIDE

Eagle and his co-workers[194] have studied the use of oxophenarsine hydrochloride given in conjunction with penicillin in the treatment of experimental rabbit syphilis. The curative doses of penicillin alone and of oxophenarsine hydrochloride alone having been determined, it was found that small fractions of the curative doses of these two spirocheticidal agents were curative when used in conjunction. The two drugs together were so much more effective than either alone that a synergistic rather than a merely additive effect was suggested. The authors say:

> 1. In early rabbit syphilis, sodium penicillin given intramuscularly twice daily for 4 days cured half the animals at a total dosage of 44,000 units per kilogram, and 90 per cent of the animals at a dosage of approximately 80,000 units per kilogram.
>
> With mapharsen alone, injected once daily for 4 days, the CD_{50}[195] dose was 2.4 mg. and the CD_{90} dose, 3.0 mg. per kilogram. A total of 1 to 1.6 mg. per kilogram cured only 1 of 21 animals.
>
> The simultaneous administration of penicillin and otherwise ineffective doses of mapharsen (0.15 mg. per kilogram daily for 4 days), reduced the CD_{50} level of penicillin from 44,000 units per kilogram to 6,100, and the CD_{90} dose from 80,000 to 32,000.
>
> With somewhat larger but still subcurative doses of arsenical (0.4 mg. per kilogram), the CD_{50} and CD_{90} dosages of penicillin were further reduced . . . respectively, one-fifty-fifth and one-twentieth the corresponding values in the absence of arsenical.
>
> 2. When sodium penicillin was injected intramuscularly 5 times daily at 4-hour intervals for 4 days, the CD_{50} dose was 1,850 units per kilogram, and the CD_{90} was 8,000 units per kilogram. The concurrent administration of mapharsen in sub-

193. Allergy to Penicillin, editorial, J. Allergy **16**:302 (Nov.) 1945.

194. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, J. Ven. Dis. Inform. **27**:3 (Jan.) 1946.

195. CD_{50} = the dose which cures 50 per cent of the animals.

curative doses (0.4 mg. per kilogram daily for 4 days) reduced the CD_{50} and the CD_{90} doses of penicillin to 320 and 1,000 units per kilogram, respectively. These were one-sixth and one-eighth of the corresponding values without arsenical.

3. It follows that penicillin and mapharsen are synergistic in the treatment of experimental syphilis, and may well be similarly synergistic in man. Under such circumstances, small amounts of penicillin supplemented by subcurative doses of mapharsen would be as effective as much larger doses of penicillin used alone. More important, the proportion of treatment failures in early syphilis cases not cured by penicillin alone may be significantly reduced by using mapharsen and penicillin in conjunction.

4. If penicillin and bismuth prove to be similarly synergistic, the optimum therapy for human syphilis may well consist of penicillin, mapharsen, and bismuth used in combination.

The clinical importance of this laboratory demonstration that penicillin and oxophenarsine hydrochloride are synergistic in action is readily apparent. Schedules of treatment in which penicillin is combined with oxophenarsine hydrochloride, a bismuth preparation or both are currently being evaluated in several of the clinics cooperating in the nation-wide penicillin study. So significant does the United States Public Health Service consider this development that at its various rapid treatment centers the concomitant administration of penicillin, oxophenarsine hydrochloride and a bismuth preparation now is used routinely.

(To Be Concluded)

News and Comment

Campaign to Combat Heart Disease.—The American Heart Association, Inc., is initiating a nationwide program of public education and information on diseases of the heart, which will call for emphasis on educational work with schools, parent-teachers' associations and other groups concerned with children because of the importance of rheumatic fever and heart disease.

The program will have as its prime purpose the dissemination of educational information to the public in a broad effort to retard the rapid increase of heart disease throughout the nation. Fatalities ascribed to diseases of the heart are greater than the total of the next five leading causes of death, i e.: cancer, accidental deaths, nephritis, pneumonia and tuberculosis. It is essential, therefore, that the public know more about the significance of blood pressure, infections, overweight, rheumatic fever and other factors which contribute to various types of heart disease.

It is estimated that there are more than 4,000,000 persons in the United States today who have heart disease. Diseases of the heart and blood vessels, including cerebral hemorrhage, accounted for 575,000 deaths in 1944.

According to recent surveys, rheumatic fever and the type of heart disease resulting from it cause almost five times as many deaths as the combined total of deaths from infantile paralysis, scarlet fever, diphtheria, measles, meningitis and whooping cough.

The educational campaign of the American Heart Association will reach its climax during National Heart Week, to begin on Feb. 9, 1947. It is expected that all branches of medicine, pharmacy, insurance, industry and many other groups interested in health and public welfare will cooperate fully.

Supporting and cooperating groups will include the following national organizations which comprise the American Council on Rheumatic Fever of the American Heart Association: the American Academy of Pediatrics, the American Association of Medical Social Workers, the American College of Physicians, the American Hospital Association, the American Medical Association, the American Nurses' Association, the American Public Health Association, the American Rheumatism Association, the American School Health Association, the National Organization for Public Health Nursing, and the National Society for Crippled Children and Adults. The collaboration of the United States Public Health Service, the Childrens Bureau, the National Tuberculosis Association and others is expected.

Local heart associations and affiliated groups in such cities as New York, Washington, San Francisco, Los Angeles, Chicago and Boston will assist in the National campaign.

Convention of the American Academy of Allergy.—The American Academy of Allergy will hold its annual convention at Hotel Pennsylvania, New York city, November 25 to 27, inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions as guests of the Academy without payment of registration fee. The program has been arranged to cover a wide variety of conditions in which allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and treatment as well as with the results of investigation and research. Advance copies of the program may be obtained by writing to the Chairman on Arrangements, Dr. Horace S. Baldwin, 136 East 64th Street, New York City, prior to November 10.

Walter M. Brickner Lecture.—The 1946 Walter M. Brickner Lecture, "Problems Relating to the Pathogenesis of Cirrhosis of the Liver," will be delivered by Dr. Arnold R. Rich, Professor of Pathology at the School of Medicine of Johns Hopkins University, on Thursday, Dec. 12, 1946, at 8:30 p. m., at the Hospital for Joint Diseases.

Members of the medical profession are invited.

Book Reviews

The Physiology of the Newborn Infant. By Clement A. Smith, M.D. Price, $5.50. Pp. 360, with illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

In the introductory chapter of this work the author states that the presentation of the physiology of the nervous system has been omitted intentionally. If this part could be presented as well as the subject matter of this book has been presented, it would be a welcome contribution.

"The Physiology of the Newborn Infant" begins with a consideration of fetal and neonatal respiration. The problem of respiratory movements before birth and the mechanism of postpartum respiration are considered. It may be advisable to mention in a later edition that differences between the values for the fetal and adult hemoglobin have not been attributed to the prosthetic group of the molecule. At the end of the chapter on fetal aspects of respiration there is a clinical summary, just as there is at the end of every chapter. These summaries form one of the most attractive features of the book.

A subdivision of the chapter on neonatal aspects of respiration is devoted to the effects and duration of anoxia at birth. The statement is made that an adult who has failed to breathe or has otherwise been totally deprived of oxygen for seven or eight minutes does not breathe again. In experiments on voluntary breath holding some subjects were able to hold their breath for as long as eleven minutes, and one at least as long as fifteen minutes, without apparent damage. In these experiments a few deep inspirations of oxygen preceded the breath holding. More recently, this period seems to have been prolonged even further.

A chapter is reserved for the circulatory system in its various aspects; another, for the morphology and the peculiarities of blood coagulation in neonatal life. A short chapter is devoted to icterus neonatorum, which is attributed to hemolysis and inadequacy of hepatic function. Metabolism and regulation of heat form the subject of another chapter, in which the author cites the observations of Benedict and Talbot on comparing pairs of contrasting subjects with similar surface areas. One of each pair was a normal infant; the other was a more or less atrophic infant who was poorly nourished and some months older. It would seem somewhat questionable whether the surface area is really similar under such conditions, if one keeps in mind the criticism of Pfaundler concerning the determination of the significant surface area.

In the chapter on the physiology of the digestive tract it is stated that the length of the intestinal tract during infancy is proportionately greater than in adult life. This may be true, although properly performed measurements, such as those which have been made in the adult by passing a tube through the intestinal tract, seem to be wanting. The subdivision on fetal and neonatal digestive secretions shows the scarcity of adequate data. It might be worth mentioning that kathepsin, which acts best in a slightly acid or neutral medium, would be of value in gastric digestion, but, after all, digestion of protein takes place chiefly in the intestine, where it encounters trypsin and the peptidases. So long as starches are not offered for digestion, the need of any amylase is problematic. Even later, it seems that the phosphorylases are more important for digestion of starches as well as for synthesis of glycogen.

A chapter each is devoted to the assimilation and metabolism of specific food substances such as proteins, carbohydrates and fat, and to the assimilation of minerals and vitamins. In another chapter renal physiology is considered. The sex hormones and the suprarenal, thyroid, pancreatic and parathyroid hormones form the subject of another chapter, while the last chapter deals with neonatal immunology. At the end of the book there is a table of normal values. This

table would seem to deserve a better place. The references to the literature appended to each chapter constitute another good feature. On the whole, they have been selected judiciously.

The aim of the author, as seen from this short survey, is a rather ambitious one. He has succeeded so well that the book may be regarded as a "must" for the pediatrician.

An Introduction to Essential Hypertension. By Richard F. Herndon, M.D. Price, $2.50. Pp. 88, with 7 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

The author of this attractively printed volume has attempted to present concisely the present conception of hypertension. He has succeeded admirably. There is occasional evidence of attempts to define the undefinable, but the attempts are good. The author presents no original work but digests evidence which has been presented by others. It is a very satisfactory digest which is characterized by forthright and forceful statements and conclusions. It is improbable that the physician whose interest in the subject is solely in the treatment of patients with hypertension will derive any more benefit from the volume than from standard textbooks. However, the student, both undergraduate and graduate, teachers and all physicians with curiosity about problems in fundamentals of disease can read it with profit. The author has placed a string through a labyrinth. With it as a guide, the reader can avoid the confusion which is ordinarily his lot when he reads much of the pertinent literature. There is occasionally the fault of oversimplification. The author errs in considering sulfocyanates and thiocyanates as different drugs.

Dr. W. C. Roentgen. By Otto Glasser. Price, $4.50. Pp. 169. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Just what qualities go into the production of a fine biography are difficult to define. If one examines, however, such eminent examples of biographic writing as Boswell's Johnson, Southey's Nelson, Lockhart's Scott, Trevelyan's Macaulay and, in more recent times, Harvey Cushing's Life of Sir William Osler, one finds in all a simple direct style, a vivid description of character and an illuminating anecdote which brings the story to life. All these qualifications are present in Glasser's admirable little biography of Roentgen. One's interest is held from the first line, and there is a happy blending of the story of a great man's scientific achievements with his personal life and character. The selection of illustrations is to the point, and the whole volume is prepared in the usual attractive style of Thomas' books.

Modern Management in Clinical Medicine. By Frederick K. Albrecht, M.D. Price, $10. Pp. 1238. Baltimore: Williams & Wilkins Company, 1946.

This large manual treats of internal medicine in a comprehensive way but more along the lines of a synopsis than of extended discussions of general subjects. There are innumerable outlines for history taking in various conditions, such as allergic disease or gastrointestinal disease, and tables of differential diagnostic points. There are many excellent illustrations. A brief section will be found on any subject, and hence the main value of the book is for reference.

Digitalis and Other Cardiotonic Drugs. By Eli Rodin Movitt, M.D. Price, $5.75. Pp. 204. New York: Oxford University Press, 1946.

The subject of digitalis has become extremely complicated in recent years through the popularization of modern purified preparations, such as Lanatoside C, Digitoxin and others. A review such as that of Movitt is therefore of great value. The botany, pharmacology, chemistry and clinical use of all the various preparations are thoroughly summarized with comprehensive references to the literature. There are many useful tables and charts and an index.

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